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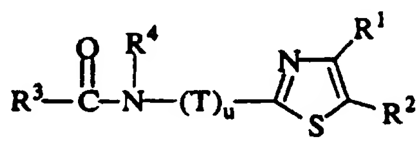
(54) Title: THIAZOLE DERIVATIVE AS PROTEIN KINASE C INHIBITORS

(57) Abstract

A thiazole compound of formula (I), wherein T is lower alkylene; u is 0 or 1; R^1 and R^2 are the same or different and are each H, or lower alkyl, etc.; R^3 is (1) or (2); R^4 is H or lower alkanoyloxy-lower alkyl, which shows inhibitory activity or protein kinase C(PKC, Ca^{2+}/phospholipid-depending serine/threonine protein phosphatase), and are useful as a protein kinase C inhibitor.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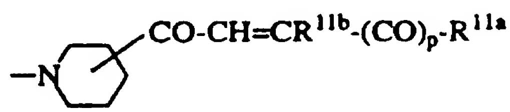
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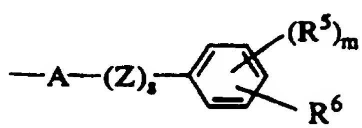
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DESCRIPTION

THIAZOLE DERIVATIVE AS PROTEIN KINASE C INHIBITORS

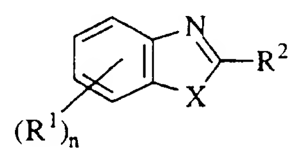
TECHNICAL FIELD

The present invention relates to a novel thiazole derivative.

BACKGROUND ART

There have hitherto been known various thiazole derivatives, among which some compounds having a somewhat similar substituents to those of the present invention are disclosed in the following literatures.

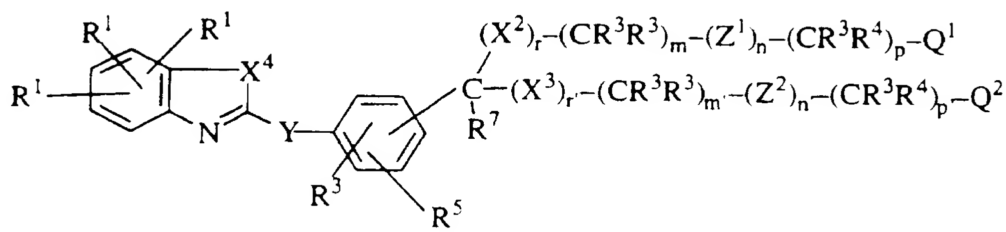
JP-A-2-306916 discloses inhibitors for platelet adhesion comprising a benzazole compound of the following formula:



wherein X is S or >N-R^3 (R^3 is H, lower alkyl, etc.); R^1 is halogen, cyano, cyano-substituted lower alkoxy, phenyl-alkyl having a substituent on benzene ring, substituted furyl-alkoxy, substituted pyrrolidinyl-alkyl, substituted amino, substituted amino-alkyl or -alkoxy, etc.; R^2 is pyrrolyl having optionally alkyl substituent, thienyl, pyridylthio-lower alkyl, phenyl group which has optionally 1 to 3 substituents selected from lower alkoxy, lower alkyl, OH, halogen, or -O-Y-NR^8R^9 (Y is lower alkylene, R^8 and R^9 are each H, lower alkyl, cycloalkyl, or both combine to form a nitrogen-containing 5- or 6-membered saturated heterocyclic group, or -$NR^{10}R^{11}$ (R^{10} and R^{11} are each H, lower alkyl, substituted phenyl, or both combine to form a heterocyclic group). However, the benzazole

compounds of this literature are significantly different from the thiazole compounds of the present invention in the substituents at 2-position of the thiazole nucleus. Besides, this literature does not disclose any compounds having protein kinase C inhibitory activities as in the present invention.

European Patent 318 084 (= U.S. Patent 4,957,932 and 5,037,840) discloses that the benzoheterazoles of the following formula are leukotriene antagonists and inhibitors of leukotriene biosynthesis and are useful as antiasthmetic, antiallergic, anti-inflammatory and cytoprotective agents.



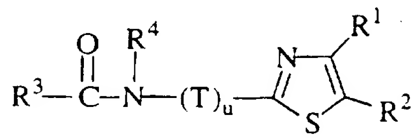
wherein R^1 is H, halogen, alkyl, etc.; R^2 is alkyl, alkenyl, etc.; R^3 is H or R^2; R^4 is H, halogen, $-NO_2$, etc.; R^5 is H, halogen, $-NO_2$, etc.; R^7 is H or alkyl; X^2 and X^3 are O, S, S(O), etc.; X^4 is NR^3, O or S; Z^1 and Z^2 are $-CONR^3-$ or $-HET(-R^3,-R^5)-$; and Q^1 and Q^2 are $-COOR^3$, $-CONHS(O)_2R^{13}$, -CN, etc. However, these benzoheterazoles of this literature are essentially different from the thiazole compounds of the present invention in the substituent at 2-position of the azole nucleus. Besides, this literature does not disclose any compounds having protein kinase C inhibitory activity.

Some thiazole or benzothiazole compounds having similar chemical structure to the benzoheterazoles of the above European Patent 318084 are also disclosed in PCT publications WO 93/21168 and WO 93/21169 and therein

it is mentioned that those compounds are useful as leukotriene antagonist, but these thiazole or benzothiazole compounds of these literatures are clearly different from the thiazole compounds of the present invention in the substituent at 2-position likewise, and further these literatures do not disclose any compound having protein kinase C inhibitory activity, either.

DISCLOSURE OF INVENTION

The thiazole derivatives of the present invention are novel compounds, and have not been disclosed in any literature, and have the following formula (1).



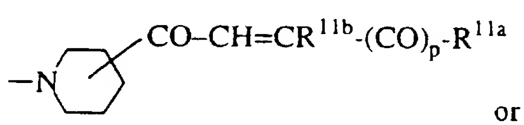
(1)

wherein T is a lower alkylene;

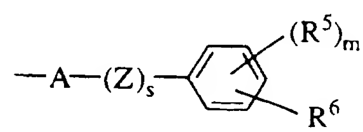
u is 0 or 1;

R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl, or both combine to form a group: $-(CH_2)_n-$ (n is 4 or 5) or to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom;

R^3 is a group of the formula:



or



wherein R^{11b}, p, R^{11a} are defined hereinafter; A is a lower alkylene; Z is O or S; s

is 0 or 1; m is 1 or 2;

R^4 is a hydrogen atom or a lower alkanoyloxy-lower alkyl;

R^5s are the same or different and are each a member selected from (a) a hydrogen atom, (b) an alkyl having optionally a hydroxy substituent, (c) a halogen atom, (d) a group of the formula: $-(O)_t-A-(CO)_\ell-NR^7R^8$ (wherein t is 0 or 1, A is a lower alkylene, ℓ is 0 or 1, and R^7 and R^8 are the same or different and are each a hydrogen atom or a lower alkyl, or both combine together with the nitrogen atom to which they bond to form a 5- to 7-membered saturated heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group being optionally substituted by a member selected from a group of the formula: $-(A)_\ell-NR^9R^{10}$ (wherein A and ℓ are as defined above, and R^9 and R^{10} are the same or different and are each a hydrogen atom or a lower alkyl, or both combine together with the nitrogen atom to which they bond to form a 5- to 7-membered saturated heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group having optionally a lower alkyl substituent), a lower alkyl having optionally a hydroxy substituent, a hydroxy group, and a lower alkanoyl), (e) a lower alkoxy-carbonyl-lower alkyl, (f) a lower alkanoyloxy-lower alkyl, (g) a lower alkoxy having optionally a halogen substituent, (h) a halogen-substituted lower alkyl, (i) a carboxyl-substituted lower alkyl, (j) a lower alkoxycarbonyl, (k) a lower alkenyloxy, (l) a phenyl-lower alkoxy, (m) a cycloalkyloxy, (n) a phenyl, (o) a phenyloxy, (p) a hydroxy, (q) a lower alkylthio, (r) a lower alkenyl, or (s) an amino having optionally a lower alkyl substituent;

R^6 is a group of the formula:

(1) $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ or (2) $-CO-C\equiv C-COR^{14}$;

p is 0 or 1;

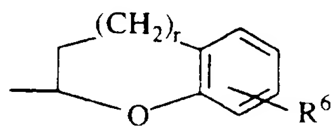
R^{11b} is a hydrogen atom or a lower alkyl;

R^{11a} is a hydroxy, a lower alkoxy, or a 5- to 10-membered, monocyclic or dicyclic, saturated or unsaturated heterocyclic group which contains 1 to 4 hetero atoms selected from a nitrogen, oxygen or sulfur atom as a ring member, said heterocyclic group having optionally 1 to 3 substituents selected from the group consisting of (i) a lower alkyl, (ii) a group of the formula: $-(B)_l-NR^{12}R^{13}$ (wherein l is as defined above, B is -CO-A- (A is as defined above), a carbonyl, or a lower alkylene, and R^{12} and R^{13} are the same or different and are each a hydrogen atom, a lower alkyl, or a lower alkyl substituted by an amino having optionally a lower alkyl substituent, or both combine together with the nitrogen atom to which they bond to form a 5- to 12-membered saturated, monocyclic, dicyclic or spirocyclic heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group having optionally a substituent selected from a lower alkyl, a lower alkoxycarbonyl, a lower alkoxy-substituted lower alkyl, an amino having optionally a lower alkyl substituent, and a hydroxy-substituted lower alkyl), (iii) a lower alkoxycarbonyl, (iv) a hydroxy-substituted lower alkyl, (v) a pyridyl being optionally substituted by a lower alkyl having optionally a halogen substituent on the pyridine ring, (vi) a halogen-substituted lower alkyl, (vii) a lower alkoxy, (viii) a cycloalkyl, (ix) a hydroxy, (x) a tetrahydropyranyloxy-substituted lower alkyl, (xi) a pyrimidyl, (xii) a lower alkoxy-substituted lower alkyl, (xiii) a carboxyl, (xiv) a phenyl-lower alkoxy, (xv) a phenyl-lower alkyl having optionally a lower alkylene-

dioxy on the phenyl ring, (xvi) a lower alkanoyloxy, and (xvii) a piperidinyl having optionally a lower alkyl substituent on the piperidine ring;

R^{14} is a hydroxy or a lower alkoxy; and

when m is 1, the groups A and R^5 may combine to form a group of the formula:



(wherein R^6 is as defined above, and r is 0, 1 or 2), or when m is 2, two R^5 groups may combine to form a lower alkylenedioxy, a lower alkylene, or a group of the formula: $-(CH_2)_2-CONH-$, or the groups R^5 and R^6 may combine to form a group of the formula: $-CO-CH(R^{28})-CH(R^{28'})-W-$ (wherein R^{28} and $R^{28'}$ are a hydrogen atom or a carboxyl group, provided that both R^{28} and R^{28} are not simultaneously a carboxyl group, and W is $-N(R^{29a})-$ or $-\overset{+}{N}(R^{29b})-R^{29b} \cdot X^-$ (wherein R^{29a} is a hydrogen atom or a lower alkyl, R^{29b} is a lower alkyl, and X is a halogen atom)),

or a salt thereof.

The thiazole derivatives of the formula (1) show inhibitory activity on protein kinase C (PKC, Ca^{2+}/phospholipid-depending serine/threonine protein phosphatase), and are useful as a protein kinase C inhibitor.

It has been proved that PKC plays an important role in the regulation of various biological functions such as the metabolism regulation, the cell prolification, the cell differentiation, the release reaction of neurotransmitter,etc.

Therefore, it is indicated that a PKC inhibitor may be useful in the prophylaxis or treatment of various diseases caused by the hyperaction of the above-mentioned biological functions being participated by PKC.

More particularly, the protein kinase C inhibitors containing as an active ingredient the present thiazole derivative are useful as an agent for treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, etc., various allergic diseases such as Crohn's disease, colitis ulcerosa, asthma, atopic dermatitis; an agent for protection of rejection in organ transplant, GVHD reaction, etc.; an agent for prophylaxis or treatment of various ischemic diseases in the organs such as heart, liver, kidney, brain, etc., acute pancreatitis, sepsis, multiple organs failure introduced by burn, ARDS, by inhibiting the production of cytokinin derived from T-cell such as IL-2, or inflammatory cytokinin such as TNF-α.

Further, by other biological functions such as cell prolification, hormone secretion, regulation of metabolism, etc. which are concerned with PKC, the protein kinase C inhibitors of the present invention are useful in the prophylaxis or treatment of cancer, diabetes, Alzheimer disease, arteriosclerosis, HIV infection, nephritis, angiitis, etc.

Each group in the above formula (1) specially means the following groups.

The lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, etc.

The lower alkoxy group includes a straight chain or branched chain C_1-

C_6 alkoxy group, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, etc.

The halogen atom is fluorine atom, chlorine atom, bromine atom or iodine atom.

The lower alkanoyloxy-substituted lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group which is substituted by 1 or 2 straight chain or branched chain C_2-C_6 alkanoyloxy groups, for example, acetyloxymethyl, 2-propionyloxyethyl, 1-butyryloxyethyl, 3-acetyloxypropyl, 4-acetyloxybutyl, 4-isobutyryloxybutyl, 5-pentanoyloxypentyl, 6-acetyloxyhexyl, 6-tert-butylcarbonyloxyhexyl, 1,1-dimethyl-2-hexanoyloxyethyl, 2-methyl-3-acetyloxypropyl, diacetyloxymethyl, 1,3-diacetyloxypropyl, etc.

The alkyl group having optionally a hydroxy substituent includes a straight chain or branched chain C_1-C_8 alkyl group which may optionally have 1 to 3 hydroxy substituents, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, heptyl, octyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 1,1-dimethyl-2-hydroxyethyl, 1,3-dihydroxypropyl, 5,5,4-trihydroxypentyl, 5-hydroxypentyl, 6-hydroxyhexyl, 1-hydroxyisopropyl, 2-methyl-3-hydroxypropyl, 7-hydroxyheptyl, 8-hydroxyoctyl, etc.

The lower alkylene group includes a straight chain or branched chain C_1-C_6 alkylene group, for example, methylene, ethylene, trimethylene, 2-methyltrimethylene, 2,2-dimethyltrimethylene, 1-methyltrimethylene, methylmethylene, ethylmethylene, tetramethylene, pentamethylene, hexamethylene, etc.

The 5- to 7-membered saturated heterocyclic group which is formed by

combining R^7 and R^8, or R^9 and R^{10} together with the adjacent nitrogen atom with or without being intervening with another nitrogen atom or an oxygen atom, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, homopiperazinyl, homomorpholino, etc.

The lower alkyl group having optionally a hydroxy substituent includes, in addition to the above lower alkyl groups, a straight chain or branched chain C_1-C_6 alkyl group which may optionally have 1 to 3 hydroxy substituents, for example, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 1,1-dimethyl-2-hydroxyethyl, 5,5,4-trihydroxypentyl, 5-hydroxypentyl, 6-hydroxyhexyl, 1-hydroxyisopropyl, 2-methyl-3-hydroxypropyl, etc.

The lower alkanoyl group includes a straight chain or branched chain C_1-C_6 alkanoyl group, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, t-butylcarbonyl, hexanoyl, etc.

The above heterocyclic group which is substituted by a group of the formula: $-(A)_\ell$-NR^9N^{10} (A is a lower alkylene group, ℓ is 0 or 1, R^9 an R^{10} are the same or different and each are a hydrogen atom or a lower alkyl group, or R^9 and R^{10} combine together with the nitrogen atom to which they bond to form a 5- or 7-membered saturated heterocyclic group with or without being intervened with another nitrogen atom or an oxygen atom, and said heterocyclic group having optionally a lower alkyl substituent), a lower alkyl group having optionally a hydroxy substituent, a hydroxy group and a lower alkanoyl group includes the above mentioned heterocyclic groups having 1 to 3

sustituents selected from a group of the formula: $-(A)_{\ell}-NR^9N^{10}$ (A is a straight chain or branched chain C_1-C_6 alkylene group, ℓ is 0 or 1, R^9 an R^{10} are the same or different and each are a hydrogen atom or a straight chain or branched chain C_1-C_6 alkyl group, or R^9 and R^{10} combine together with the nitrogen atom to which they bond to form a 5- or 7-membered saturated heterocyclic group with or without being intervened with another nitrogen atom or an oxygen atom, and said heterocyclic group having optionally 1 to 3 straight chain or branched chain C_1-C_6 alkyl substituents), a straight chain or branched chain alkyl group having optionally 1 to 3 hydroxy substituents, a hydroxy group and a straight chain or branched chain C_1-C_6 alkanoyl group, for example, 4-methyl-piperazinyl, 2-(4-methyl-1-piperazinyl)methylmorpholino, 4-(4-methyl-1-piperazinyl)piperidinyl, 4-methylhomopiperazinyl, 4-(2-hydroxyethyl)-piperazinyl, 4-morpholinopiperidinyl, 2-[(1-pyrrolidinyl)methyl]morpholino, 4-hydroxypiperidinyl, 4-acetylpiperazinyl, 4-dimethylaminopiperidinyl, 4-(4-methyl-1-homopiperazinyl)piperidinyl, 4-(4,5-dimethyl-1-homopiperazinyl)-piperidinyl, 4-(3-methyl-4-ethyl-1-piperazinyl)piperidnyl, 4-(3-methyl-4-n-propyl-1-piperazinyl)piperidinyl, 4-(3,4-dimethyl-1-piperazinyl)piperidinyl, 4-(4-isopropyl-3-methylpiperazinyl)piperidinyl, 4-(4-methyl-3-isopropylpiperazinyl)-piperidinyl, 2-methylpyrrolidinyl, 3-ethylpyrrolidinyl, 2,3-dimethylpyrrolidinyl, 2,3,4-trimethylpyrrolidinyl, 2-propylmorpholino, 3-(1-pyrrolidinyl)pyrrolidinyl, 3-isopropylmorpholino, 2,3-dimethylmorpholino, 4-n-butylpiperidinyl, 3,4,5-trimethylpiperidinyl, 3-pentylpiperidinyl, 4-methylhomopiperazinyl, 4,5-dimethylhomopiperazinyl, 4-hexylhomopiperazinyl, 3-methyl-4-ethyl-

piperazinyl, 3-methyl-4-n-propyl-1-piperazinyl, 3,4-dimethylpiperazinyl, 4-isopropyl-3-methylpiperazinyl, 4-methyl-3-isopropylpiperazinyl, 4-methyl-homomorpholino, 3-propionylpyrrolidinyl, 4-butyrylpiperidinyl, 4-pentanoyl-piperazinyl, 3-hexanoylmorpholino, 4-acetylhomopiperazinyl, 3-hydroxy-morpholino, 4-hydroxyhomopiperazinyl, 4-hydroxypiperazinyl, 3-hydroxy-pyrrolidinyl, 3-hydroxymethylpyrrolidinyl, 3-(3-hydroxypropyl)morpholino, 2-hydroxymethylhomomorpholino, 2-(4-methyl-1-piperazinyl)methylhomo-morpholino, 4-(1,3-dihydroxy-2-propyl)piperazinyl, 4-ethylhomopiperazinyl, 3-(4-methyl-1-homopiperazinyl)pyrrolidinyl, 4-methyl-3-(1-piperidinyl)methyl-piperazinyl, 4-methyl-3-(4-methyl-1-homopiperazinyl)methylpiperazinyl, 4-methyl-3-(4-methyl-1-piperazinyl)methylpiperazinyl, etc.

The above heterocyclic group substituted by a lower alkyl group includes the above heterocyclic groups substituted by 1 to 3 straight chain or branched chain C_1-C_6 alkyl groups, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 3-ethylpyrrolidinyl, 2-propylpyrrolidinyl, 1-methyl-pyrrolidinyl, 3,4,5-trimethylpiperidinyl, 4-butylpiperidinyl, 3-pentylmorpholino, 4-ethylhomopiperazinyl, 4-methylhomopiperazinyl, 4-hexylpiperazinyl, 4-methylhomopiperazinyl, 4,5-dimethylhomopiperazinyl, 3-methyl-4-ethyl-piperazinyl, 3-methyl-4-n-propylpiperazinyl, 4-isopropyl-3-methylpiperazinyl, 4-methyl-3-isopropylpiperazinyl, 4-methylhomomorpholino, etc.

The lower alkoxycarbonyl-substituted lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group which is substituted by a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms, for example, methoxycarbonylmethyl, 3-methoxycarbonylpropyl, ethoxy-

carbonylmethyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonylpentyl, 6-propoxycarbonylhexyl, 1,1-dimethyl-2-butoxycarbonylethyl, 2-methyl-3-tert-butoxycarbonylpropyl, 2-pentyloxycarbonylethyl, hexyloxycarbonylmethyl, etc.

The lower alkanoyloxy-substituted lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group which is substituted by a straight chain or branched chain C_2-C_6 alkanoyloxy group, for example, acetyloxymethyl, 2-propionyloxyethyl, 1-butyryloxyethyl, 3-acetyloxypropyl, 4-acetyloxybutyl, 4-isobutyryloxybutyl, 5-pentanoyloxypentyl, 6-acetyloxyhexyl, 6-tert-butylcarbonyloxyhexyl, 1,1-dimethyl-2-hexanoyloxyethyl, 2-methyl-3-acetyloxypropyl, etc.

The lower alkoxy group having optionally a halogen substituent includes a straight chain or branched chain C_1-C_6 alkoxy group which optionally has 1 to 3 halogen substituents, for example, in addition to the above lower alkoxy groups, trifluoromethoxy, trichloromethoxy, chloromethoxy, bromomethoxy, fluoromethoxy, iodomethoxy, difluoromethoxy, dibromomethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 3-chloropropoxy, 2,3-dichloropropoxy, 4,4,4-trichlorobutoxy, 4-fluorobutoxy, 5-chloropentyloxy, 3-chloro-2-methylpropoxy, 6-bromohexyloxy, 5,6-dichlorohexyloxy, etc.

The halogen-substituted lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group, which has 1 to 3 halogen substituents, for example, trifluoromethyl, trichloromethyl, chloromethyl, bromomethyl, fluoromethyl, iodomethyl, difluoromethyl, dibromomethyl, 2-chloroethyl, 2,2,2-trifluoro-

ethyl, 2,2,2-trichloroethyl, 3-chloropropyl, 2,3-dichloropropyl, 4,4,4-trichlorobutyl, 4-fluorobutyl, 5-chloropentyl, 3-chloro-2-methylpropyl, 6-bromohexyl, 5,6-dichlorohexyl, etc.

The carboxy-substituted lower alkyl group includes a carboxyalkyl group wherein the alkyl moiety is a straight chain or branched chain C_1-C_6 alkyl group, for example, carboxymethyl, 2-carboxyethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, 2-methyl-3-carboxypropyl, etc.

The lower alkoxycarbonyl group includes a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.

The aminocarbonyl-substituted lower alkoxy group having optionally a lower alkyl group includes a straight chain or branched chain C_1-C_6 alkoxy group, which has an aminocarbonyl group having optionally 1 to 2 straight chain or branched chain C_1-C_6 alkyl group, for example, aminocarbonylmethoxy, 2-aminocarbonylethoxy, 1-aminocarbonylethoxy, 3-aminocarbonylpropoxy, 4-aminocarbonylbutoxy, 5-aminocarbonylpentyloxy, 6-aminocarbonylhexyloxy, 1,1-dimethyl-2-aminocarbonylethoxy, 2-methyl-3-aminocarbonylpropoxy, methylaminocarbonylmethoxy, 1-ethylaminocarbonylethoxy, 2-propylaminocarbonylethoxy, 1-ethylaminocarbonylethoxy, 2-propylaminocarbonylethoxy, 3-isopropylaminocarbonylpropoxy, 4-butylaminocarbonylbutoxy, 5-pentylaminocarbonylpentyloxy, 6-hexylaminocarbonylhexyloxy,

dimethylaminocarbonylmethoxy, 2-diethylaminocarbonylethoxy, 2-dimethylaminocarbonylethoxy, (N-ethyl-N-propylamino)carbonylmethoxy, 2-(N-methyl-N-hexylamino)carbonylethoxy, etc.

The amino-substituted lower alkyl group having optionally a lower alkyl substituent includes a straight chain or branched chain C_1-C_6 alkyl group which is substituted by an amino group having optionally 1 to 2 C_1-C_6 alkyl substituents, for example, aminomethyl, 2-aminoethyl, 1-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, 6-aminohexyl, 1,1-dimethyl-2-aminoethyl, 2-methyl-3-aminopropyl, methylaminomethyl, 1-ethylaminoethyl, 2-propylaminoethyl, 3-isopropylaminopropyl, 4-butylaminobutyl 5-pentylaminopentyl, 6-hexylaminohexyl, dimethylaminomethyl, (N-ethyl-N-propylamino)methyl, 2-(N-methyl-N-hexylamino)ethyl, etc.

The 5- to 12-membered saturated heteromonocyclic, heterobicyclic or heterospirocyclic group which is formed by combining R^{12} and R^{13} together with the adjacent nitrogen atom to which they bond with or without being intervened with another nitrogen atom or an oxygen atom includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, homopiperazinyl, homomorpholino, 1,4-diazabicyclo[4.3.0]nonyl, 1,4-diazabicyclo[4.4.0]decyl, 1,4-diazaspiro[5.5]undecyl, etc.

The lower alkoxy-substituted lower alkyl group includes a straight chain or branched chain C_1-C_6 alkyl group which has 1 to 3 straight chain or branched chain C_1-C_6 alkoxy groups, for example, methoxymethyl 3-methoxypropyl, ethoxymethyl, 2-methoxyethyl, 3-ethoxypropyl, 4-ethoxybutyl, 5-isopropoxypentyl, 6-propoxyhexyl, 1,1-dimethyl-2-butoxyethyl, 2-methyl-3-

tert-butoxypropyl, 2-pentyloxyethyl, hexyloxymethyl, etc.

The amino group having optionally a lower alkyl substituent includes an amino group having optionally 1 to 2 straight chain or branched chain C_1-C_6 alkyl groups, for example, amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, pentylamino, hexylamino, dimethylamino, diethylamino, dipropylamino, dibutylamino, dipentylamino, dihexylamino, N-methyl-N-ethylamino, N-ethyl-N-propylamino, N-methyl-N-butylamino, N-methyl-N-hexylamino, etc.

The above heterocyclic group having a substituent selected from a lower alkyl group, a lower alkoxy-substituted lower alkyl group, a lower alkoxy-carbonyl group, an amino group having optionally a lower alkyl substituent and a hydroxy-substituted lower alkyl group includes the above mentioned hetero-cyclic groups having 1 to 3 substituents selected from a straight chain or branched chain C_1-C_6 alkyl group, a straight chain or branched chain C_1-C_6 alkyl group which has 1 to 3 straight chain or branched chain C_1-C_6 alkoxy group, a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, an amino group having optionally 1 to 2 straight chain or branched chain C_1-C_6 alkyl groups and a straight chain or branched chain C_1-C_6 alkyl group which has 1 to 3 hydroxy substituents, for example, 4-methylpiperazinyl, 3,4-dimethylpiperazinyl, 4-ethylpiperazinyl, 4-methylhomopiperazinyl, 4-dimethylaminopiperidinyl, 4-tert-butoxycarbonyl-homopiperazinyl, 4-n-butylhomopiperazinyl, 4-(2-hydroxyethyl)piperazinyl, 3-methylpiperazinyl, 4-(1,3-dihydroxy-2-propyl)piperazinyl, 4-(1,3-dihydroxy-2-propyl)homopiperazinyl, 3,4,5-trimethylpiperazinyl, 4-isopropylpiperazinyl,

3,3,4-trimethylpiperazinyl, 4,5-dimethylhomopiperazinyl, 3-methyl-4-ethyl-piperazinyl, 3-methyl-4-n-propylpiperazinyl, 3-n-propyl-4-methylpiperazinyl, 3-methyl-4-isopropylpiperazinyl, 3-ethyl-4-methylpiperazinyl, 3-methyl-4-(2-methoxyethyl)piperazinyl, 3-methyl-4-(2-hydroxyethyl)piperazinyl, 3-isopropyl-4-methylpiperazinyl, 4-methyl-1,4-diazasprio[5.5]undecyl, 3-amino-1,4-diazabicyclo[4.4.0]decyl, 5-hydroxymethyl-1,4-diazabicyclo[4.3.0]nonyl, 3-ethoxycarbonylhomomorpholino, 3-diethylaminomorpholino, 3-methoxy-methylpyrrolidinyl, etc.

The lower alkyl group having optionally a halogen substituent includes, for example, in addition to the above lower alkyl groups and halogen-substituted lower alkyl groups.

The pyridyl group having optionally a lower alkyl substituent which may optionally have a halogen substituent on the pyridine ring includes a pyridyl group having 1 to 3 straight chain or branched chain C_1-C_6 alkyl groups which may optionally 1 to 3 halogen substituents on the pyridine ring, for example, pyridyl, 3-methylpyridyl, 4-ethylpyridyl, 2-propylpyridyl, 3-butylpyridyl, 4-pentylpyridyl, 4-hexylpyridyl, 3,4-dimethylpyridyl, 3,4,5-trimethylpyridyl, 3-trifluoromethylpyridyl, 2-chloromethylpyridyl, 4-(5-bromohexyl)pyridyl, 3-iodomethylpyridyl, 4-(2,2,2,-trifluoroethyl)pyridyl, 4-(5,6-dichlorohexyl)pyridyl, etc.

The cycloalkyl group includes a C_3-C_8 cycloalkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

The tetrahydropyranyloxy-substituted lower alkyl group includes a tetrahydropyranyloxy-substituted alkyl group wherein the alkyl moiety is a

straight chain or branched chain C_1-C_6 alkyl group, for example, (2-tetrahydropyranyl)oxymethyl, 2-(3-tetrahydropyranyl)oxyethyl, 1-(4-tetrahydropyranyl)-oxyethyl, 3-(2-tetrahydropyranyl)oxypropyl, 4-(3-tetrahydropyranyl)oxybutyl, 5-(4-tetrahydropyranyl)oxypentyl, 6-(2-tetrahydropyranyl)oxyhexyl, 1,1-dimethyl-2-(3-tetrahydropyranyl)oxyethyl, 2-methyl-3-(4-tetrahydropyranyl)-oxypropyl, etc.

The phenyl-lower alkyl group includes a phenylalkyl group wherein the alkyl moiety is a straight chain or branched chain C_1-C_6 alkyl group, for example, benzyl, 2-phenylethyl, 1-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, 6-phenylhexyl, 1,1-dimethyl-2-phenylethyl, 2-methyl-3-phenyl-propyl, etc.

The phenyl-lower alkoxy group includes a phenylalkoxy group wherein the alkoxy moiety is a straight chain or branched chain C_1-C_6 alkoxy group, for example, benzyloxy, 2-phenylethoxy, 1-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, 5-phenylpentyloxy, 6-phenylhexyloxy, 1,1-dimethyl-2-phenyl-ethoxy, 2-methyl-3-phenylpropoxy, etc.

The lower alkanoyloxy group includes a straight chain or branched chain C_1-C_6 alkanoyloxy group, for example, formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pentanoyloxy, tert-butylcarbonyloxy, hexanoyloxy, etc.

The piperidinyl group having optionally a lower alkyl substituent on the piperidine ring includes a piperidinyl group having optionally a straight chain or branched chain C_1-C_6 alkyl group, for example, piperidinyl, 1-methyl-4-piperidinyl, 1-ethyl-3-piperidinyl, 1-ethyl-2-piperidinyl, 1-propyl-4-piperidinyl, 1-

butyl-4-piperidinyl, 1-pentyl-4-piperidinyl, 1-hexyl-4-piperidinyl, 1-isobutyl-3-piperidinyl, 1-tert-butyl-2-piperidinyl, etc.

The phenyl-lower alkyl group having optionally a lower alkylenedioxy substituent on the phenyl ring includes a phenylalkyl group having optionally a straight chain or branched chain C_1-C_4 alkylenedioxy group on the phenyl ring wherein the alkyl moiety is a straight chain or branched chain C_1-C_6 alkyl group, in addition to the above phenyl-lower alkyl groups, for example, 3,4-methylenedioxybenzyl, 2-(3,4-ethylenedioxyphenyl)ethyl, 1-(3,4-ethylene-dioxyphenyl)ethyl, 3-(2,3-trimethylenedioxyphenyl)propyl, 4-(3,4-tetra-methylenedioxyphenyl)butyl, 5-(3,4-methylenedioxyphenyl)pentyl, 6-(2,3-trimethylenedioxyphenyl)hexyl, etc.

The lower alkylenedioxy group includes a straight chain or branched chain C_1-C_4 alkylenedioxy group, for example, methylenedioxy, ethylenedioxy, trimethylenedioxy, tetramethylenedioxy, etc.

The 5- to 10-membered, saturated or unsaturated heteromonocyclic or heterobicyclic residue having 1 to 4 heteroatoms selected from a nitrogen atom, an oxygen atom and a sulfur atom includes, for example, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, 1-azabicyclooctyl, homopiperazinyl, homo-morpholino, 1,4-diazabicyclo[4.3.0]nonyl, 1,4-diazabicyclo[4.4.0]decyl, pyridyl, 1,2,5,6-tetrahydropyridyl, thienyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, 1,3,4-triazoly, quinolyl, 1,4-dihydroquinolyl, benzothiazolyl, pyrazyl, pyrimidyl, pyridazinyl, pyrrolyl, pyrrolinyl, carbostyril, 1,3-dioxolanyl, thiomorpholino, 3,4-dihydro-carbostyril, 1,2,3,4-tetrahydroquinolyl, 2,3,4,5-tetrahydrofuryl, indolyl, isoindolyl, 3H-indolyl, indolinyl, indolidinyl, indazolyl, benzimidazolyl, benzoxazolyl,

imidazolinyl, imidazolidinyl, isoquinolyl, naphthylidinyl, quinazolidinyl, quinoxalinyl, cinnolinyl, phthalazinyl, chromanyl, isoindolinyl, isochromanyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, thienyl, imidazolyl, pyrazolidinyl, benzofuryl, 2,3-dihydrobenzo[b]furyl, benzothienyl, tetrahydropyranyl, 4H-chromenyl, 1H-indazolyl, 2-imidazolinyl, 2-pyrrolinyl, furyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, pyranyl, pyrazolidinyl, 2-pyrazolinyl, quinuclidinyl, 1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 1,4-benzothiazinyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinoxalinyl, 1,3-dithia-2,4-dihydronaphthalenyl, 1,4-dithia-naphthalenyl, 2,5-dihydrofurano[3.4-c]pyridyl, 2,3,4,5,6,7-hexahydro-1H-azepinyl, 1,2,3,4,5,6,7,8-octahydroazocinyl, 1,2,3,4,5,6,-tetrahydrooxepinyl, 1,3-dioxolanyl, 3,4,5,6-tetrahydro-2H-pyranyl, 5,6-dihydro-2H-pyranyl, etc.

The above heterocyclic groups having 1 to 3 substituents selected from (i) a lower alkyl group; (ii) a group: $-(B)_{\ell}-NR^{12}R^{13}$ (ℓ is the same as defined above, B is a group: –CO–A– (A is the same as defined above), a carbonyl group or a lower alkylene group, R^{12} and R^{13} are the same or different, and each are a hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group having optionally a lower alkyl substituent, or combine together with the adjacent nitrogen atom to which they bond to form a 5- to 12-membered saturated heteromonocyclic, heterobicyclic or spiro-cyclic hetero ring with or without being intervened with another nitrogen atom or an oxygen atom, said heterocyclic group may optionally have a substituent selected from a lower alkyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkyl group, an amino group having optionally a lower alkyl substituent and a

hydroxy-substituted lower alkyl group); (iii) a lower alkoxycarbonyl group; (iv) a hydroxy-substituted lower alkyl group; (v) a pyridyl group being optionally substituted by a lower alkyl group having optionally a halogen substituent on the pyridine ring; (vi) a halogen-substituted lower alkyl group; (vii) a lower alkoxy group; (viii) a cycloalkyl group; (ix) a hydroxy group; (x) a tetrahydro-pyranyloxy-substituted lower alkyl group; (xi) a pyrimidyl group; (xii) a lower alkoxy-substituted lower alkyl group; (xiii) a carboxyl group; (xiv) a phenyl-lower alkoxy group; (xv) a phenyl-lower alkyl group having optionally a lower alkylenedioxy substituent on the phenyl ring; (xvi) a lower alkanoyloxy group; and (xvii) a piperidinyl group having optionally a lower alkyl substituent on the piperidine ring includes the above heterocyclic groups having 1 to 3 substituents selected from (i) a straight chain or branched chain C_1-C_6 alkyl group; (ii) a group: $-(B)_\ell$-$NR^{12}R^{13}$ (ℓ is the same as defined above, B is a group: –CO–A– (A is the same as defined above), a carbonyl group or a straight chain or branched chain C_1-C_6 alkylene group, R^{12} and R^{13} are the same or different, and each are a hydrogen atom, a straight chain or branched chain C_1-C_6 alkyl group, or a straight chain or branched chain C_1-C_6 alkyl group which has an amino group having optionally 1 to 2 straight chain or branched chain alkyl substituents, or both combine together with the adjacent nitrogen atom to which they bond to form a 5- to 12-membered saturated heteromonocyclic, heterobicyclic or sprio-cyclic hetero ring with or without being intervened with another nitrogen atom or an oxygen atom, said heterocyclic group may optionally have 1 to 3 substituents selected from a straight chain or branched chain C_1-C_6 alkyl group, a straight chain or branched chain C_1-C_6 alkyl group

which has 1 to 3 straight chain or branched chain C_1-C_6 alkoxy substituents, a straight chain or branched chain alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety, an amino group having optionally 1 to 2 straight chain or branched chain C_1-C_6 alkyl substituent and a straight chain or branched chain C_1-C_6 alkyl group having 1 to 3 hydroxy substituents); (iii) an alkoxycarbonyl group having 1 to 6 carbon atoms in the alkoxy moiety; (iv) a straight chain or branched chain C_1-C_6 alkyl group having 1 to 3 hydroxy substituents; (v) a pyridyl group having optionally 1 to 3 straight chain or branched chain C_1-C_6 alkyl groups which have optionally 1 to 3 halogen substituents on the pyridine ring; (vi) a straight chain or branched chain C_1-C_6 alkyl group having 1 to 3 halogen substituents; (vii) a straight chain or branched chain C_1-C_6 alkoxy group; (viii) a C_3-C_8 cycloalkyl group; (ix) a hydroxy group; (x) a tetrahydropyranyloxy-substituted alkyl group wherein the alkyl moiety is a straight chain or branched chain C_1-C_6 alkyl group; (xi) a pyrimidyl group; (xii) a straight chain or branched chain C_1-C_6 alkyl group having 1 to 3 straight chain or branched chain C_1-C_6 alkoxy substituents; (xiii) a carboxyl group; (xiv) a phenyl alkoxy group wherein the alkoxy moiety is a straight chain or branched chain C_1-C_6 alkoxy group; (xv) a phenylalkyl group having optionally a straight chain or branched chain C_1-C_4 alkylenedioxy substituent on the phenyl ring, wherein the alkyl moiety is a straight chain or branched chain C_1-C_6 alkyl group; (xvi) a straight chain or branched chain C_1-C_6 alkanoyloxy group; and (xvii) a piperidinyl group having optionally 1 to 3

straight chain or branched chain C_1-C_6 alkyl substituents on the piperidine ring, for example, 4-methylpiperazinyl, 4-(4-methyl-1-piperazinyl)piperidinyl, 2-(4-methyl-1-piperazinylmethyl)morpholino, 2-(4-methyl-1-piperazinylmethyl)-pyrrolidinyl, 3-(4-methyl-1-piperazinyl)pyrrolidinyl, 1-ethyl-1,2,3,4-tetrazolyl, 1-tert-butoxycarbonylpiperidinyl, 1-methylpiperidinyl, 2,2-dimethyl-1,3-dioxolanyl, 4-(3,4-dimethyl-1-piperazinyl)piperidinyl, 4-(4-ethyl-1-piperazinyl)-piperidinyl, 4-[N-(2-diethylaminoethyl)-N-methylamino]piperidinyl, 4-(4-methyl-1-homopiperazinyl)piperidinyl, 2-(4-ethyl-1-piperazinylmethyl)morpholino, 4-dimethylaminopiperidinyl, 2-morpholinomethylpyrrolidinyl, 4-(1-pyrrolidinyl)-piperdinyl, 4-isopentylpiperazinyl, 4-(2-hydroxyethyl)piperazinyl, 2-(1-pyrrolidinylmethyl)morpholino, 4-morpholinopiperidinyl, 2-aminomethyl-morphlino, 1-dimethylaminomethylcarbonylpiperidinyl, 1-methylimidazolyl, 4-(2-pyridyl)piperazinyl, 4-(3,4-methylenedioxybenzyl)piperazinyl, 1-(4-chloro-butyl)-1,2,3,4-tetrazolyl, 2-methoxycarbonylpyridyl, 2-carboxypyridyl, 4-isopropylpyridyl, 4-hydroxypiperidinyl, 2-methyl-3-hydroxy-2,5-dihydrofuran-[3,4-c]pyridyl, 1-cyclohexyl-1,2,34-tetrazolyl, 3-(4-methyl-1-piperazinyl)-pyrrolidinyl, 1-[(3-3,4,5,6-tetrahydro-2H-pyranyl)methyl]-1,2,3,4-tetrazolyl, 1-(3-chloropropyl)-1,2,3,4-tetrazolyl, 2-carbamoylpyrrolidinyl, 4-(3-trifluoromethyl-2-pyridyl)piperazinyl, 4-benzylpiperidinyl, 4-n-butyl-1,2,3,4-tetrazolyl, 4-carbamoylpiperidinyl, 2-(4-methyl-1-piperazinyl)homomorpholino, 2-methyl-morpholino, 2-methoxymethylmorpholino, 2-chloromethylmorpholino, 2-hydroxymethylmorpholino, 2-n-butoxymethylmorpholino, 2-(4-methyl-1-homopiperazinylmethyl)morpholino, 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolyl, 2-(4-methyl-1-homopiperazinylmethyl)homomorpholino, 2-chloromethylhomomorpholino, 2-hydroxymethylhomomorpholino, 4-hydroxy-

piperazinyl, 2-methoxymethyl-1,2,3,4,5,6-hexahydrooxepinyl, 4-(2-phenyl-ethoxy)piperidinyl, 4-benzyloxypiperidinyl, 4-hydroxy-3- methylpiperazinyl, 4-methylhomopiperazinyl, 4-acetyloxypiperazinyl, 4-methoxypiperazinyl, 4-(4-tert-butoxycarbonyl-1-homopiperazinyl)piperidnyl, 4-(4-n-butyl-1-homo-piperazinyl)piperidinyl, 4-(1-methyl-4-piperidinyl)homopiperazinyl, 3-(4-methyl-1-homopiperazinyl)piperidinyl, 2-(4-dimethylamino-1-piperidinylmethyl)-morpholino, 2-(4-methyl-1-piperazinylmethyl)homomorpholino, 2-[4-(2-hydroxyethyl)-1-piperazinylmethyl]morpholino, 4-(3-methyl-1-piperazinyl)-piperidinyl, 4-(4-ethyl-1-homopiperazinyl)piperidinyl, 3-(4-methyl-1-homo-piperazinyl)pyrrolidinyl, 4-[4-(1,3-dihydroxy-2-propyl)-1-piperazinyl]-piperidinyl, 4-[4-(1,3-dihydoxy-2-propyl)-1-homopiperazinyl]piperidnyl, 4-methyl-3-(1-piperidinylmethyl)piperazinyl, 4-methyl-3-(4-methyl-1-piperazinyl-methyl)piperazinyl, 4-methyl-3-(4-methyl-1-homopiperazinylmethyl)piperazinyl, 3,4,5-trimethoxypiperazinyl, 4-isopropylpiperazinyl, 4-(1,4-diazabicyclo[4.3.0]-nonyl)piperidinyl, (3,3,4-trimethyl-1-piperazinyl)piperidinyl, 4-(1,4-diazabicyclo-[4.4.0]decyl)piperidinyl, 4-(3-methyl-4-ethyl-1-piperazinyl)piperidinyl, 4-(3-methyl-4-propyl-1-piperazinyl)piperidinyl, 4-(3-propyl-4-methyl-1-piperazinyl)-piperidinyl, 4-(3-methyl-4-isopropyl-1-piperazinyl)piperidinyl, 4-(3-ethyl-4-methyl-1-piperazinyl)piperidinyl, 4-[3-methyl-4-(2-methoxyethyl)-1-piperazinyl]-piperidinyl, 4-[3-methyl-4-(2-hydroxyethyl)-1-piperazinyl]piperidinyl, 4-(4-methyl-1-1,4-diazaspiro[5.5]undecyl)piperidinyl, 4-(4-methyl-3-isopropyl-1-piperazinyl)piperidinyl, 4-(2-pyrimidyl)piperazinyl, etc.

The lower alkenyloxy group includes a C_2-C_6 straight chain or branched chain alkenyloxy group, for example, vinyloxy, 1-methylvinyloxy, 2,2-dimethyl-vinyloxy, 1,2-dimethylvinyloxy, 1-propylvinyloxy, allyloxy, 2-butenyloxy, 3-

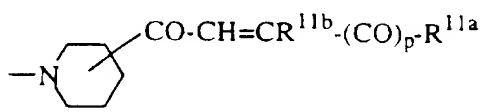
butenyloxy, 1-ethylvinyloxy, 1-methylallyloxyl, 1-pentenyloxy, 2-pentenyloxy, 2-hexenyloxy, 3-methyl-1-butenyloxy, 1-butenyloxy, etc.

The cycloalkyloxy group includes a C_3-C_8 cycloalkyloxy group, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclooctyloxy, etc.

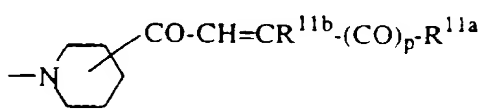
The lower alkylthio group includes a C_1-C_6 straight chain or branched chain alkylthio group, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio, pentylthio, hexylthio, etc.

The lower alkenyl group includes a C_2-C_6 straight chain or branched chain alkenyl group, for example, vinyl, 1-methylvintyl, 2,2-dimethylvinyl, 1,2-dimethylvinyl, 1-propenylvinyl, allyl, 2-butenyl, 3-butenyl, 1-ethylvinyl, 1-methylallyl, 1-pentenyl, 2-pentenyl, 2-hexenyl, 3-methyl-1-butenyl, 1-butenyl, etc.

The present invention specifically includes the following compounds.

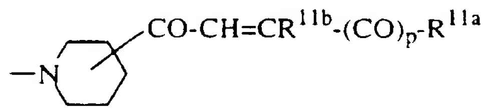
(1) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula: 

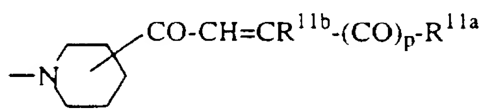
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(2) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula: 

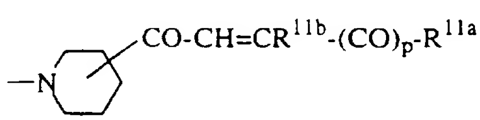
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group,

and u is 0, or a salt thereof.

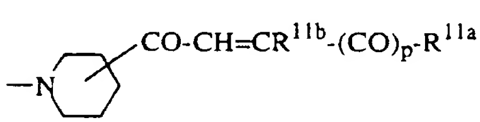
(3) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(4) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group, and u is 1, or a salt thereof.

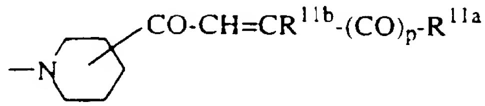
(5) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(6) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

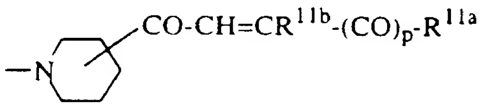
 (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(7) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



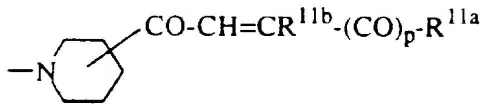
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(8) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



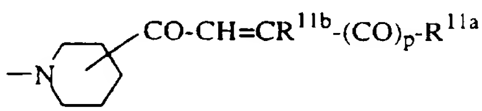
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(9) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

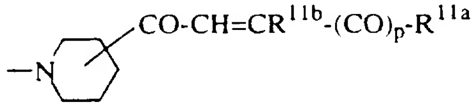
(10) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



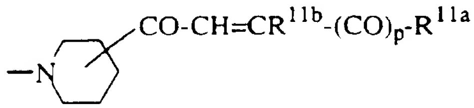
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

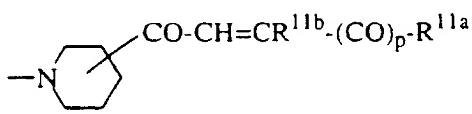
(11) A thiazole derivative of the formula (1) wherein R^1 and R^2

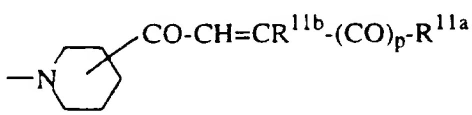
combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:


(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

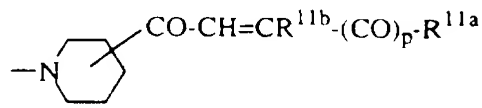
(12) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:


(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

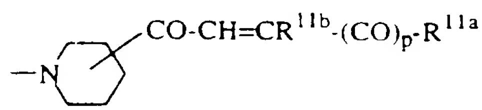
(13) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(14) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom,R^3 is a group of the formula:  (R^{11b}, p and R^{11a} are

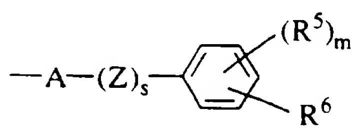
the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(15) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula: 

(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

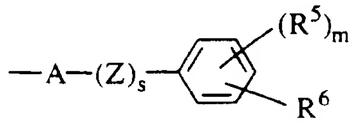
(16) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula: 

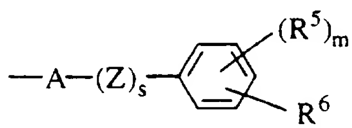
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

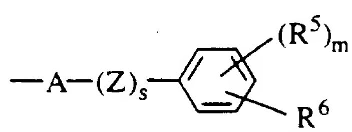
(17) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula: 

(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a

hydrogen atom, and u is 0, or a salt thereof.

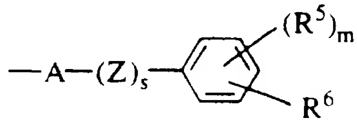
(18) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(19) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

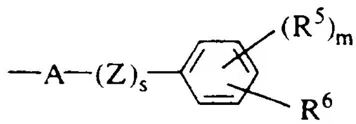
(20) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(21) A thiazole derivative of the formula (1) wherein R^1 and R^2

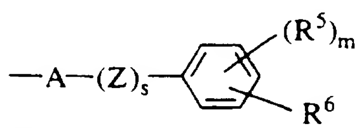
combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

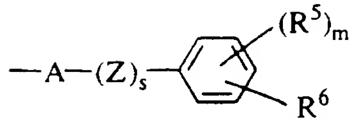
(22) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

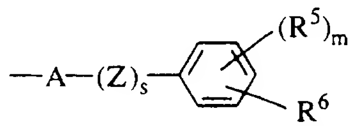

(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

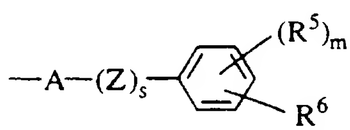
(23) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

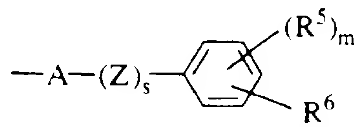

(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

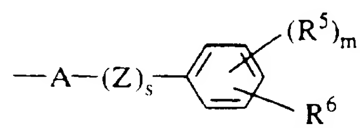
(24) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

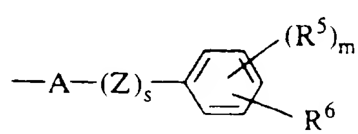
group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(31) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

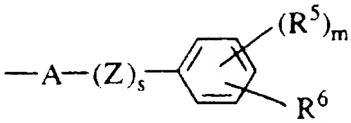
(32) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(33) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different, and each are a hyrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

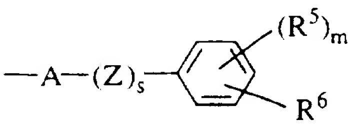
(34) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different, and each are a hyrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(35) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different, and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

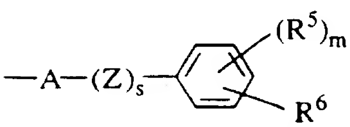
(36) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different, and each are a hydrogen atom or a lower alkyl group, R^3 is a


(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

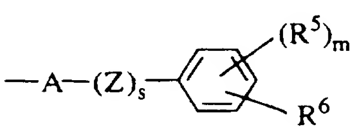
(25) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(26) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

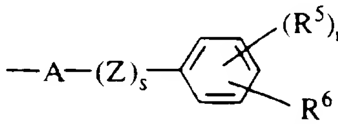

(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(27) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$

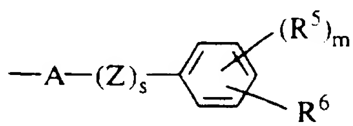
(R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(28) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



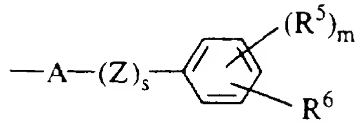
(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(29) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:

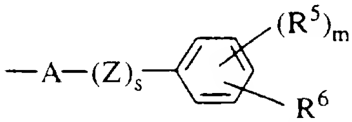


(s is 0, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m, A and Z are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

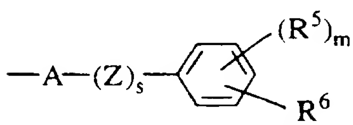
(30) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a

group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

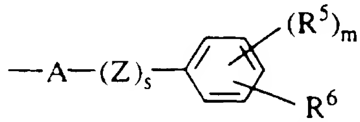
(37) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

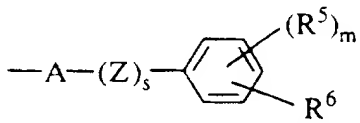
(38) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

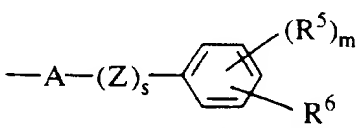
(39) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

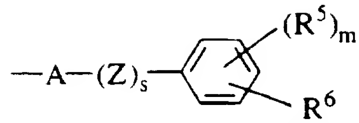
(40) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

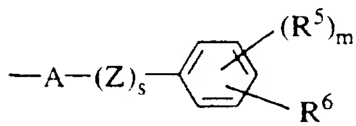
(41) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

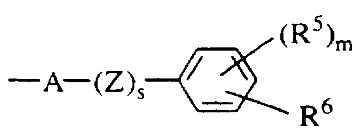
(42) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

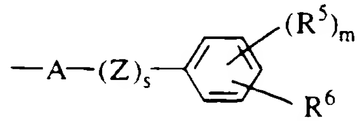
(43) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

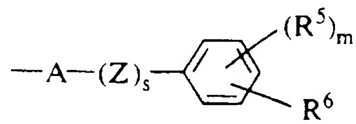
 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

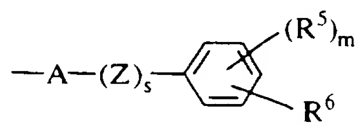
(44) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

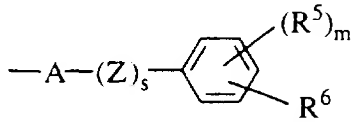
 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

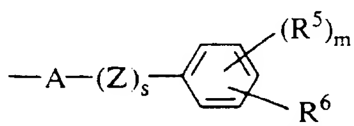
(45) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a

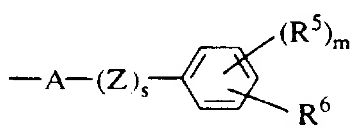
group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

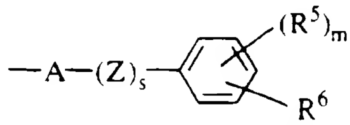
(46) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

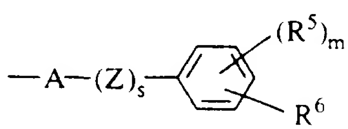
(47) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(48) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

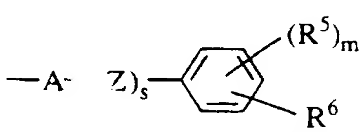
(49) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(50) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(51) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

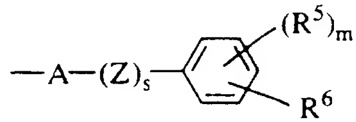
(52) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(53) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

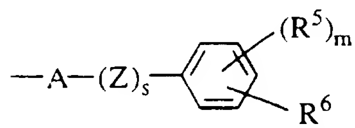
 (s is 1, Z is a sulfur atom, R^6 is a group: –CO- l$=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(54) A thiazole derivative of the formula (1) wherein R^1 and R^2

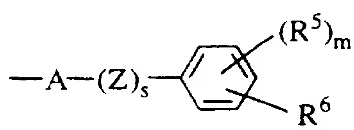
combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

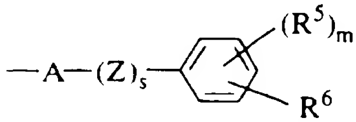
(55) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

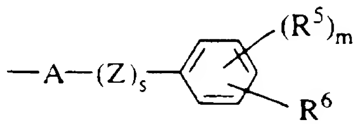
(56) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

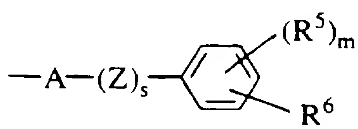
(57) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

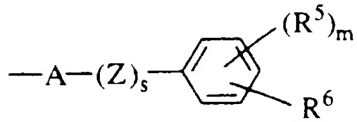
(58) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

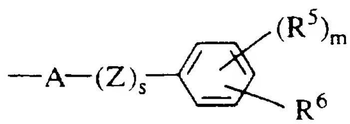
 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

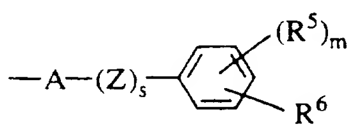
(59) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

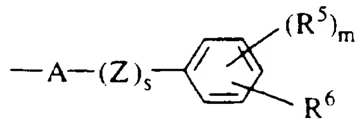
 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

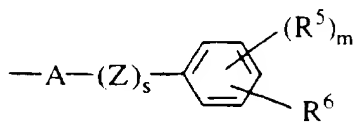
(60) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

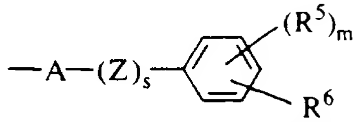
 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(61) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

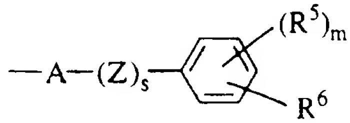
(62) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

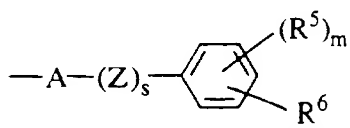
(63) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

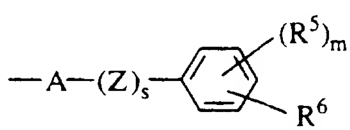
(64) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ (R^{11b}, p and R^{11a} are the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(65) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-C\equiv C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A

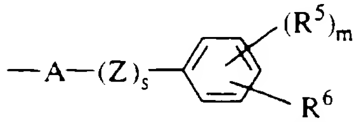
are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(66) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

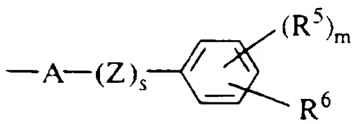
(67) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(68) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

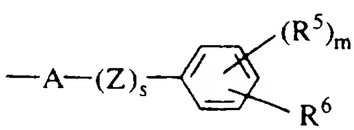
(69) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

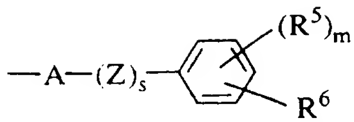
(70) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

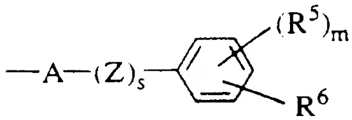
(71) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:


(s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

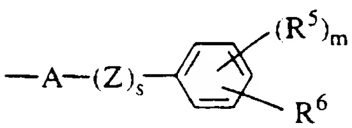
(72) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

 (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

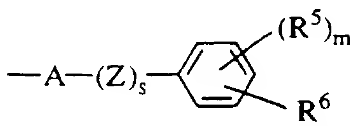
(73) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(74) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

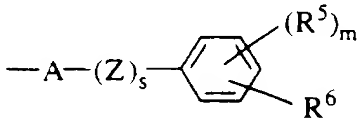
 (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(75) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the

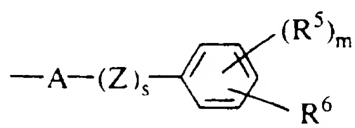
formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(76) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



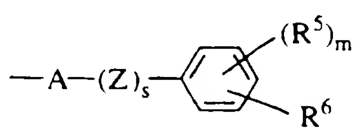
(s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(77) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:



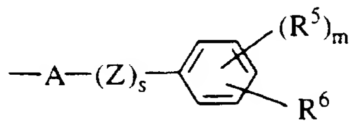
(s is 0, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

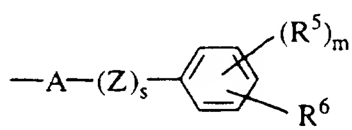
(78) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:



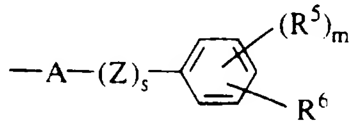
(s is 0, R^6 is a group:

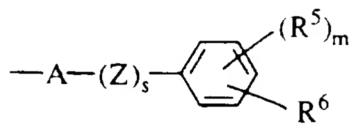
–CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

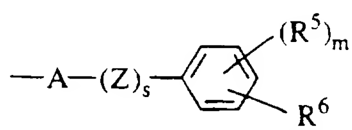
(79) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 0, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

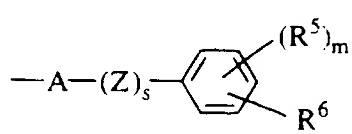
(80) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 0, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, Z, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(81) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a

group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C\equiv C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

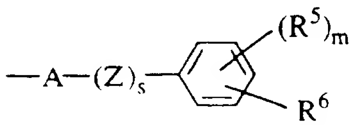
(82) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C\equiv C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(83) A thiazole derivative [illegible]e formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C\equiv C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(84) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is

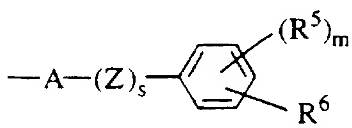
a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(85) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



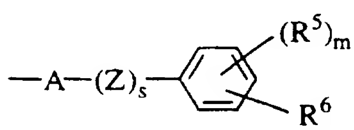
(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(86) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

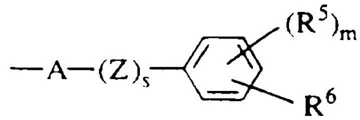
(87) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A

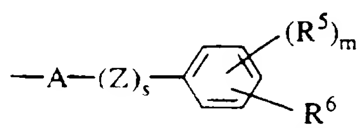
are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(88) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:



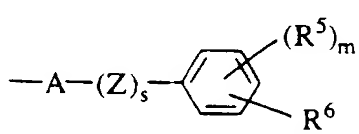
(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(89) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

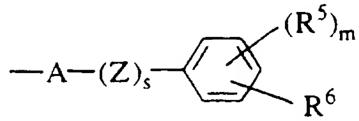
(90) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:



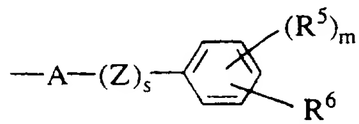
(s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl

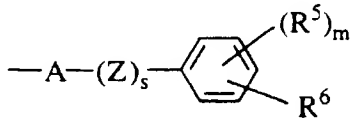
group and u is 0, or a salt thereof.

(91) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

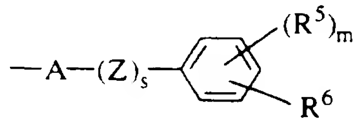
 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

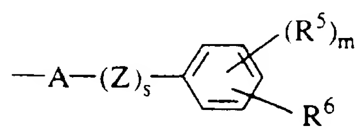
(92) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

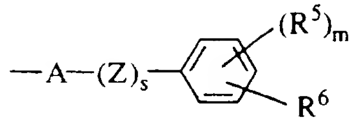
(93) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is

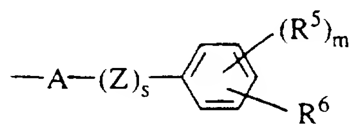
0, or a salt thereof.

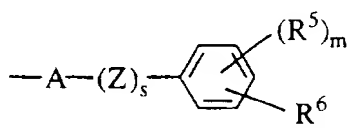
(94) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

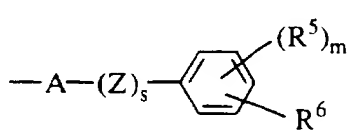
(95) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(96) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a

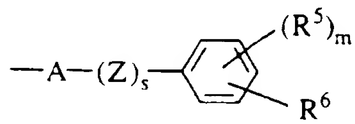
group of the formula:  (s is 1, Z is an oxygen atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(97) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

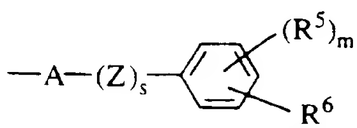
(98) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

(99) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is

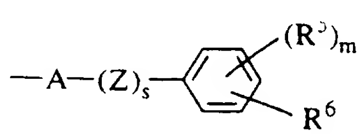
a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(100) A thiazole derivative of the formula (1) wherein R^1 and R^2 are the same or different and each are a hydrogen atom or a lower alkyl group, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(101) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: –$(CH_2)_n$– (n is 4), R^3 is a group of the formula:

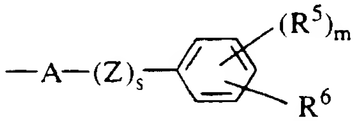
 (s is 1, Z is a sulfur atom, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(102) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: –$(CH_2)_n$– (n is 4), R^3 is a group of the formula:

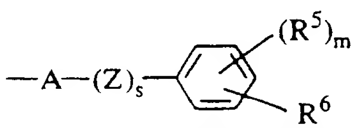
 (s is 1, Z is a sulfur atom, R^6 is a group: –CO–C≡C–COR^{14} (R^{14} is the same as defined in the formula (1)), R^5, m and A

are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

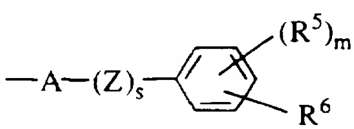
(103) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:


(s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(104) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4), R^3 is a group of the formula:

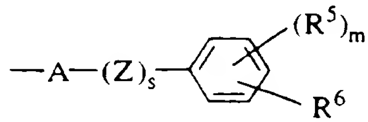

(s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

(105) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

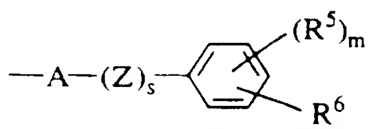

(s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a

salt thereof.

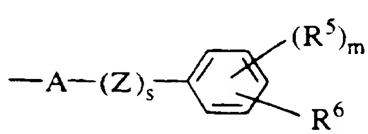
(106) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

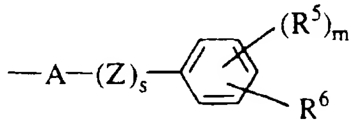
(107) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

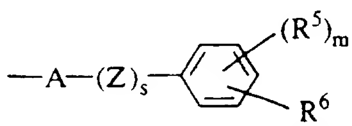
 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

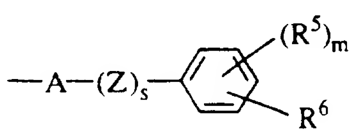
(108) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5), R^3 is a group of the formula:

 (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

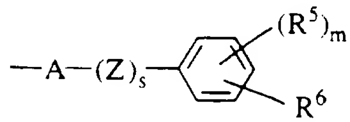
(109) A thiazole derivative of the formula (1) wherein R^1 and R^2

combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 0, or a salt thereof.

(110) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 0, or a salt thereof.

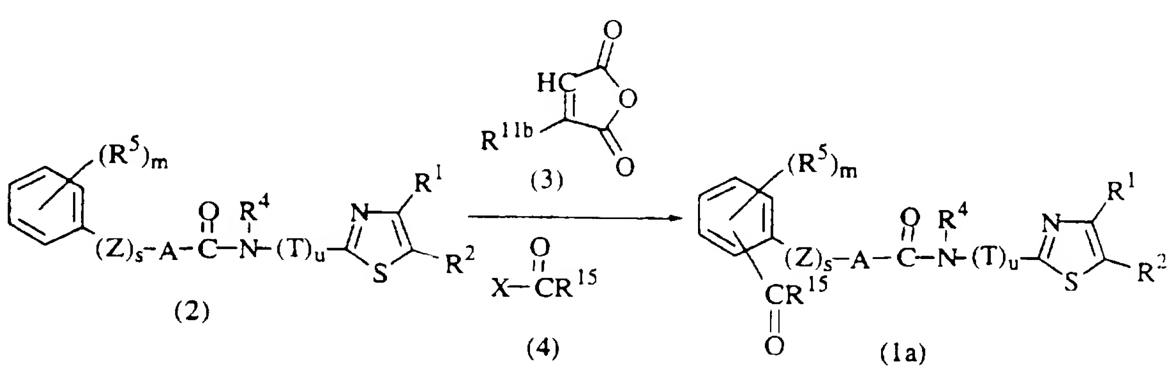
(111) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m

and A are the same as defined in the formula (1)), R^4 is a hydrogen atom, and u is 1, or a salt thereof.

(112) A thiazole derivative of the formula (1) wherein R^1 and R^2 combine to form a benzene ring which may optionally have a substituent selected from a lower alkyl group, a lower alkoxy group, a nitro group, an amino group having optionally a lower alkyl substituent and a halogen atom, R^3 is a group of the formula:  (s is 1, Z is a sulfur atom, R^6 is a group: $-CO-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in the formula (1)), R^5, m and A are the same as defined in the formula (1)), R^4 is a lower alkanoyloxy-lower alkyl group and u is 1, or a salt thereof.

The compounds of the present invention of the formula (1) may be prepared by various processes, but preferably prepared by the following processes.

Reaction Scheme-1



wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined above, R^{15} is a group: $-CH{=}C(R^{11b})(COR^{16})$ (R^{11b} is the same as defined above, and R^{16} is a

hydroxy group or a lower alkoxy group), or a group: $-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined above), and X is a halogen atom.

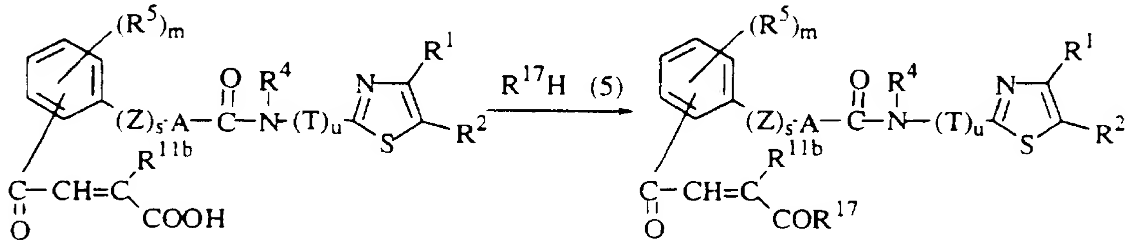
The reaction between the compound (2) and the compound (3) or the compound (4) is called Friedel-Crafts Reaction, and carried out in the presence of a Lewis acid in a suitable solvent. The Lewis acid may be any conventional Lewis acids which are used in this kind of Friedel-Crafts Reaction, and is, for example, aluminum chloride, zinc chloride, iron chloride, stannous chloride, boron tribromide, boron trifluoride, conc. sulfuric acid, etc. The solvent may be, for example, carbon disulfide, aromatic hydrocarbons such as nitrobenzene, chlorobenzene, halogenated hydrocarbons such as dichloromethane, dichloroethane, carbon tetrachloride, tetrachloroethane, aliphatic nitro compounds such as nitroethane, nitromethane, or a mixture of these solvents. The compound (3) and the compound (4) are used each at least in an equimolar amount, preferably in an amount of 1 to 5 moles, to 1 mole of the compound (2). The Lewis acid is usually used in an amount of 1 to 6 moles, to 1 mole of the compound (2). The reaction is usually carried out at 0 to 120°C, preferably at 0 to 70°C, for about 0.5 to 24 hours.

The compound wherein R^{15} is a group: $-CH=C(R^{11b})(COR^{16})$, and the double bond thereof shows a cis-configuration can be isomerized into the compound wherein the double bond shows a trans-configuration by heating it at about 50°C to 100°C in dimethylformamide.

The compound (1a) wherein R^{15} is a group: $-CH=C(R^{11b})(COR^{16})$ or a group: $-C{\equiv}C-COR^{14}$, and R^{16} and R^{14} are both a lower alkoxy group may be converted into a compound (1a) wherein a corresponding R^{16} and R^{14} are a

hydroxy group, by treating it under the same conditions as in the reaction of converting the compound (1d) into the compound (1e) in Reaction Scheme 4, described hereinbelow.

Reaction Scheme-2



(1b) (1c)

wherein R^1, R^2, R^4, R^5, R^{11b}, Z, m, s, T, u and A are the same as defined above, R^{17} is the heterocyclic residues as defined for R^{11a} but having at least one $-N\langle$ in the heterocyclic nucleus.

The process of Reaction Scheme-2 is a conventional amido bond producing reaction, and is carried out by reacting the thiazole compound (1b) and the amine compound (5). The amido bond producing reaction can be carried out under the same conditions as those of the conventional amino bond producing reaction, for example,

(a) a mixed acid anhydride process, i.e. a process of reacting the carboxylic acid compound (1b) with an alkyl halocarbonate to form a mixed acid anhydride and reacting the resultant with the amine compound (5);

(b) an activated ester process, i.e. a process of converting the carboxylic acid compound (1b) into an activated ester such as p-nitrophenyl ester, N-hydroxysuccinimide ester, 1-hydroxybenzotriazole ester, etc., and

reacting the resultant with the amine compound (5);

(c) a carbodiimide process, i.e. a process of condensing the carboxylic acid compound (1b) and the amine compound (5) in the presence of an activating agent such as dicyclohexylcarbodiimide, carbonyldiimidazole, etc.;

(d) other processes, i.e. a process of converting the carboxylic acid compound (1b) into a carboxylic anhydride by treating it with a dehydrating agent such as acetic anhydride, and reacting the resultant with the amine compound (5); a process of reacting an ester of the carboxylic acid compound (1b) with a lower alcohol and the amine compound (5) at high temperature under high pressure; a process of reacting an acid halide compound of the carboxylic acid compound (1b), i.e. a carboxylic acid halide, with the amine compound (5).

The mixed acid anhydride used in the above mixed acid anhydride process (a) is obtained by the known Schötten-Baumann reaction, and the reaction product is used without isolating from the reaction mixture for the reaction with the amine compound (5) to give the desired compound (1) of the present invention. The Schötten-Baumann reaction is usually carried out in the presence of a basic compound. The basic compound is any conventional compounds used for the Schötten-Baumann reaction and includes, for example, organic basic compounds such as triethylamine, trimethylamine, pyridine, dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine, 1,5-diazabicyclo-[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc., and inorganic basic compounds such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, etc. The reaction is usually carried out at a temperature

from about –20°C to about 100°C, preferably at a temperature of –20°C to about 50°C, for about 5 minutes to about 10 hours, preferably for 5 minutes to about 2 hours.

The reaction between the mixed acid anhydride thus obtained and the amine compound (5) is usually carried out at a temperature of –20°C to about 150°C, preferably at a temperature of –20°C to about 50°C, for about 5 minutes to about 35 hours, preferably for about 5 minutes to 30 hours. The mixed acid anhydride process is usually carried out in a solvent in the presence of a basic compound. The basic compounds may be any basic compounds used in the above Schötten-Baumann reaction. The solvent may be any conventional solvents which are usually used in the mixed acid anhydride process and includes, for example, halogenated hydrocarbons (e.g. chloroform, dichloromethane, dichloroethane, etc.), aromatic hydrocarbons (e.g. benzene, p-chlorobenzene, toluene, xylene, etc.), ethers (e.g. diethyl ether, diisopropyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g. methyl acetate, ethyl acetate, etc.), aprotic polar solvents (e.g. N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, hexamethylphosphoric triamide, 1-methyl-2-pyrrolidinone (NMP), etc.), or a mixture of these solvents. The alkyl halocarbonate used in the mixed acid anhydride process includes, for example, methyl chloroformate, methyl bromoformate, ethyl chloroformate, ethyl bromoformate, isobutyl chloroformate, and the like. In said process, the carboxylic acid compound (1b), the alkyl halocarbonate ester and the amine compound (5) are usually used in equimolar amount each, but preferably the alkyl halocarbonate ester and the amine compound (5) are used in an amount of about 1 to 1.5 mole, to 1 mole of the carboxylic acid (1b).

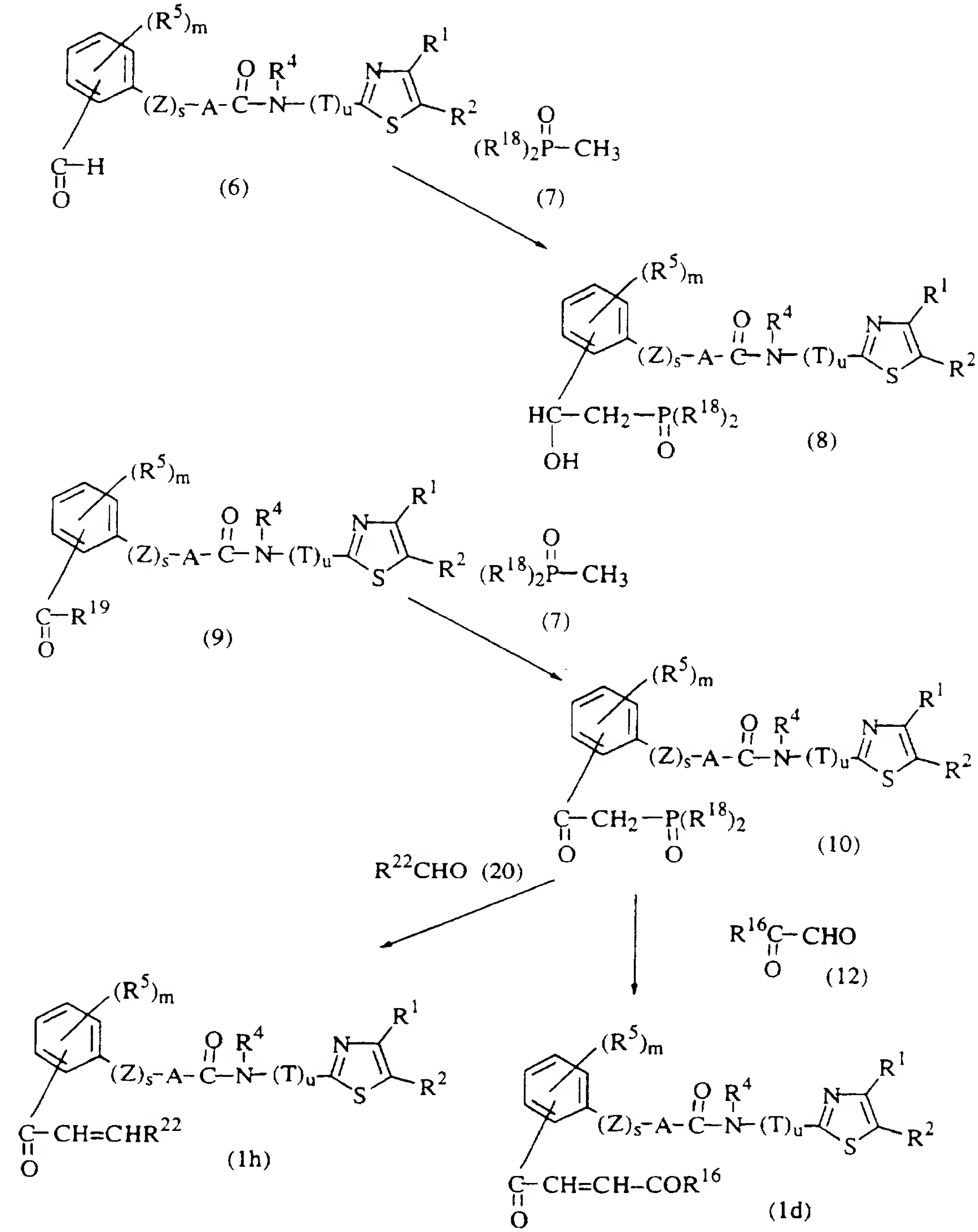
Among the above other processes (d), in case of the process of reacting the carboxylic acid halide with the amine compound (5), the reaction is usually carried out in the presence of a basic compound in a suitable solvent. The basic compound is any conventional basic compounds and includes, for example, in addition to the basic compounds used in the above mentioned Schötten-Baumann reaction, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, and the like. The solvent includes, for example, in addition to the solvents used in the mixed acid anhydride process, alcohols (e.g. methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethylcellosolve, methylcellosolve, etc.), pyridine, acetone, water, or a mixture of two or more these solvents, and the like. The amount of the amine compound (5) and the carboxylic acid halide is not critical, but the amine compound (5) is usually used at least in equimolar amount, preferably in an amount of about 1 to 5 moles, to 1 mole of the carboxylic acid halide. The reaction is usually carried out at a temperature of about –70°C to about 180°C, preferably at a temperature of about –50°C to about 150°C, for about 5 minutes to about 30 hours.

Besides, the amido bond producing reaction of Reaction Scheme-2 may also be carried out by reacting the carboxylic acid compound (1b) and the amine compound (5) in the presence of a condensing agent such as phosphorus compounds (e.g. phenylphosphine-2,2'-dithiopyridine, diphenylphosphinyl chloride, phenyl-N-phenylphosphoramide chloridate, diethyl cyanophosphate, diethyl cyanophosphate, diphenylphosphoryl azide, N,N'-bis(2-oxo-3-oxa-zolidinyl)phosphinic chloride, etc.).

The reaction is usually carried out in the presence of the same solvent and the same basic compound which can be used in the above reaction of the

carboxylic acid halide compound and the amine compound (5). The reaction is usually carried out at a temperature of –20°C to about 150°C, preferably at a temperature of 0°C to about 100°C, for about 5 minutes to about 30 hours. The condensing agent and the amine compound (5) are used at least in equimolar amount, preferably in an amount of about 1 to 2 moles, to 1 mole of the carboxylic acid compound (1b).

Reaction Scheme-3



wherein R^1, R^2, R^3, R^4, R^5, Z, m, s, T, u, R^{16} and A are the same as defined above,

R^{18} and R^{19} are a lower alkoxy group, and R^{22} is the same as defined below.

The reaction of the compound (6) and the compound (7) is carried out in the presence of a basic compound in a suitable solvent. The basic compound includes inorganic basic compounds such as metal sodium, metal potassium, sodium hydride, sodium amide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, etc., organic basic compounds such as alkali metal alkoxide (e.g., sodium methylate, sodium ethylate, potassium t-butoxide), an alkyl lithium, aryl lithium or lithium amide (e.g., methyl lithium, n-butyl lithium, phenyl lithium, lithium diisopropylamide), pyridine, piperidine, quinoline, triethylamine, N,N-dimethylaniline, etc. The solvent may be any one which does not disturb the reaction, for example, water, ethers (e.g., diethyl ether, dioxane, tetrahydrofuran, monoglyme, diglyme, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), aliphatic hydrocarbons (e.g., n-hexane, heptane, cyclohexane, etc.), amines (e.g., pyridine, N,N-dimethylaniline, etc), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), ureas (e.g., N,N'-dimethylpropylene urea (DMPU), etc.), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, or a mixture of these solvents. The reaction is usually carried out at –80°C to 150°C, preferably at about –80° to 120°C, for 0.5 to about 15 hours.

The compound (7) is usually used at least in an equimolar amount, preferably in an amount of 1 to 5 moles, to 1 mole of the compound (6).

The reaction of converting the compound (8) into the compound (10) is

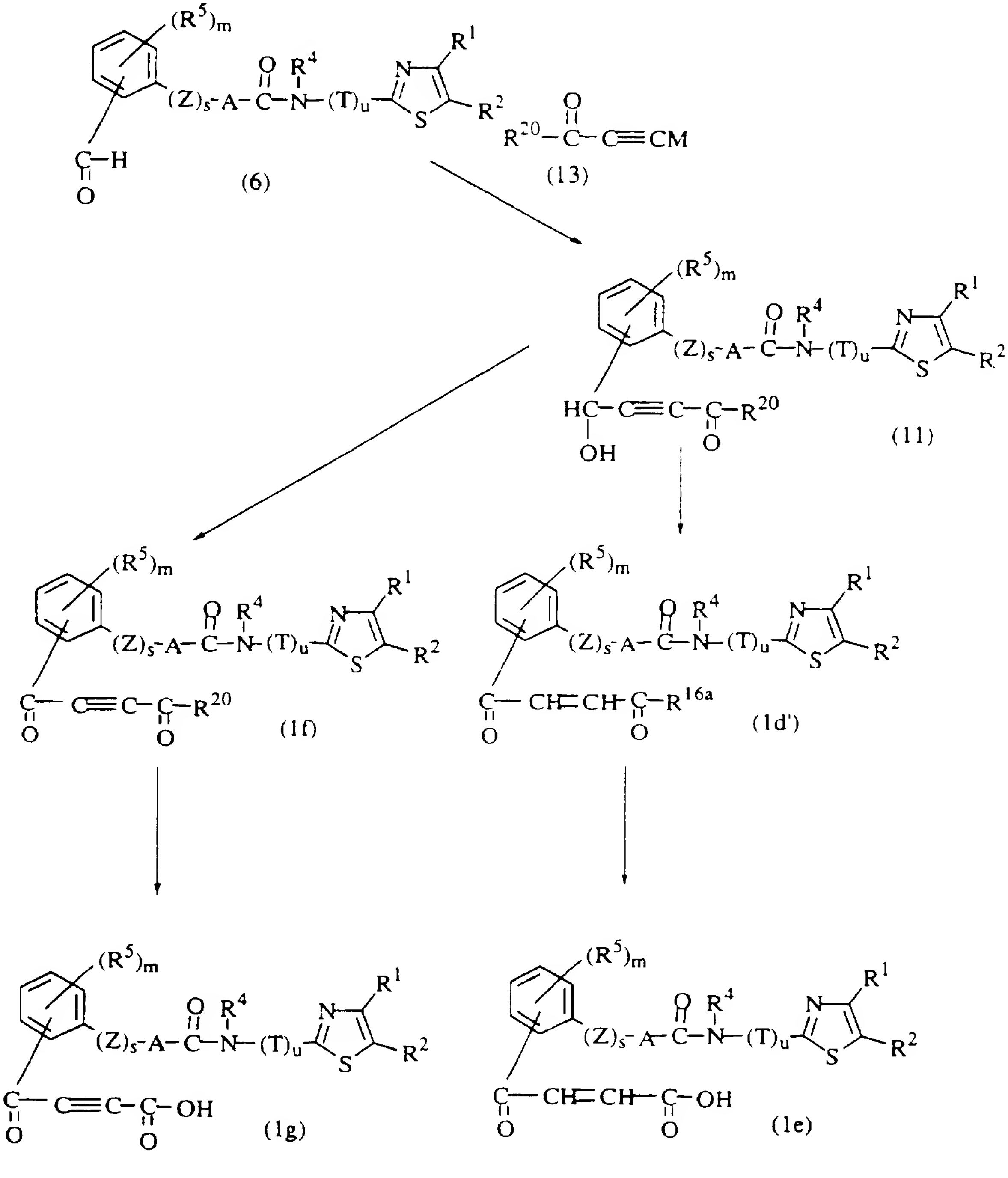
carried out in the presence of an oxidizing agent in a suitable solvent. The oxidizing agent includes, for example, benzoquinones (e.g., 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)), pyridinium chromates (e.g., pyridinium chlorochromate, pyridium dichlorochromate, etc.), dimethylsulfoxide-oxazolyl chloride, dichromic acid, dichromates (e.g. sodium dichromate, potassium dichromate, etc.), permanganic acid, permanganates (e.g. potassium permanganate, sodium permanganate, etc.), manganese dioxide, etc. The solvent includes, for example, water, organic acids (e.g. formic acid, acetic acid, trifluoroacetic acid, etc.), alcohols (e.g. methanol, ethanol, etc.), halogenated hydrocarbons (e.g. chloroform, dichloromethane, etc.), ethers (e.g., tetrahydrofuran, diethyl ether, dioxane, etc.), dimethylsulfoxide, dimethylformamide, or a mixture of these solvents. The oxidizing agent is preferably used in an excess amount to the amount of the starting compound. The above reaction is usually carried out at 0°C to 200°C, preferably at 0°C to about 150°C, for 1 hour to about 10 hours.

The reaction of the compound (9) and the compound (7) is carried out under the same conditions as those in the reaction of the compound (6) and the compound (7).

The reaction of the compound (10) and the compound (12) is carried out under the same conditions as those in the reaction of the compound (6) and the compound (7).

The reaction of the compound (10) and the compound (20) is carried out under the same conditions as those in the reaction of the compound (6) and the compound (7).

Reaction Scheme-4



wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined above, R^{20} is a lower alkoxy group, M is an alkali metal such as lithium, sodium, potassium, etc.,

and R^{16a} is a lower alkoxy group.

The reaction of the compound (6) and the compound (13) is carried out in the presence of a basic compound in a suitable solvent, at –80°C to room temperature, for 5 minutes to 6 hours. The solvent may be, for example, ethers (e.g., diethyl ether, dioxane, tetrahydrofuran, etc.), aromatic hydrocarbons (e.g., benzene, toluene, etc.), saturated hydrocarbons (e.g., hexane, heptane, pentane, cyclohexane, etc.), ureas (e.g., N,N'-dimethylpropyleneurea (DMPU), etc.). The basic compounds are the same ones which are used in the reaction of the compound (6) and the compound (7) in the above Reaction Scheme-3. The compound (13) is usually used at least in equimolar amount, preferably in an amount of 1 to 5 moles, to 1 mole of the compound (6).

The reaction of converting the compound (11) into the compound (1d') is carried out in the presence of a basic compound in a suitable solvent. The basic compound may be organic basic compound such as triethylamine, trimethylamine, diisopropylamine, tri-n-butylamine, ethylamine, pyridine, dimethylaniline, N-methylmorpholine, 4-dimethylaminopyridine, DBN, DBU, DABCO, etc. The solvent includes, for example, water, alcohols (e.g., ethanol, methanol, isopropanol, etc.), dimethylformamide, diemthylsulfoxide, hexamethylphosphoric triamide, or a mixture of these solvents. The reaction is usually carried out at room temperature to 150°C, preferably at room temperature to 100°C, for about 1 to 5 hours.

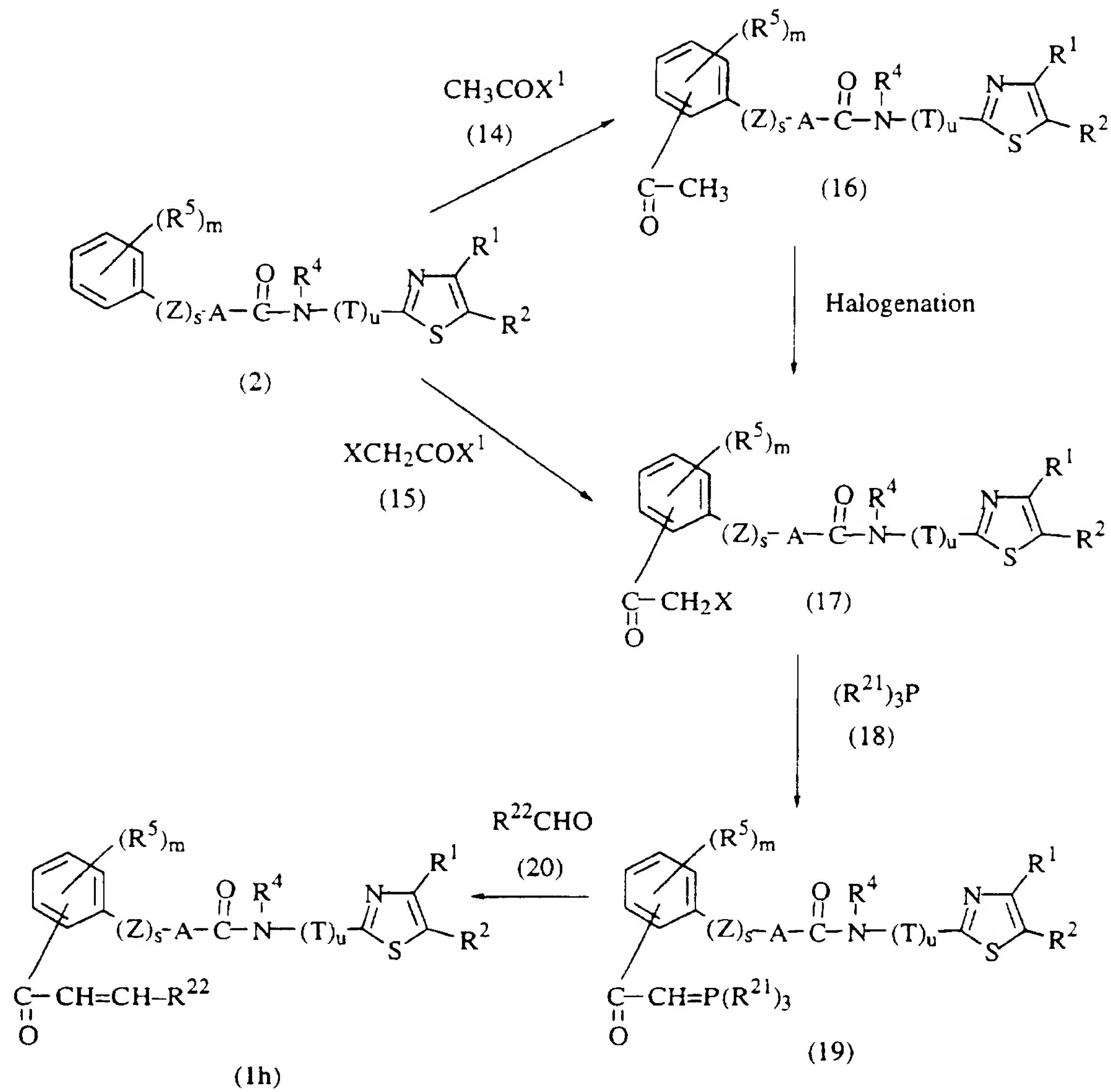
The reaction of converting the compound (11) into the compound (1f) is carried out under the same conditions as those in the reaction of converting the compound (8) into the compound (10) in the above Reaction Scheme-3.

The reaction of converting the compound (1d') into the compound (1e) is

carried out in the presence of an acid or a basic compound in a suitable solvent, or without a solvent. The solvent includes, for example, water, lower alcohols (e.g., ethanol, methanol, isopropanol, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), ethers (e.g., dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), fatty acids (e.g., acetic acid, formic acid, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid, etc.), organic acids (e.g., formic acid, acetic acid, trifluoric acid, aromatic sulfuric acids, etc.). The basic compound includes, for example, an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, etc.), etc. The reaction is usually carried out at room temperature to about 200°C, preferably at room temperature to 150°C, for about 10 minutes to 25 hours.

The reaction of converting the compound (1f) into the compound (1g) is carried out under the same conditions as those in the reaction of converting the compound (1d') into the compound (1e) as mentioned above.

Reaction Scheme-5



wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined above, X^1 is a halogen atom, R^{21} is a phenyl group, R^{22} is a 5- to 10-membered, saturated or unsaturated heteromonocyclic, heterobicyclic residue (said heterocyclic residue optionally having 1 to 3 substituents selected from (i) a lower alkyl group; (ii) a group: $-(B)_\ell$-$NR^{12}R^{13}$ (ℓ is the same as defined above, B is a group: –CO–A– (A

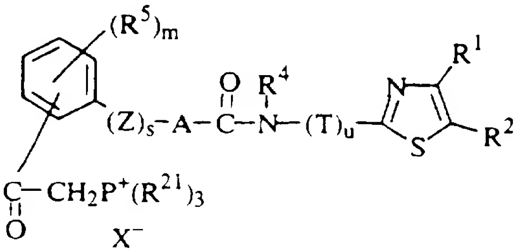
is the same as defined above), a carbonyl group or a lower alkylene group, R^{12} and R^{13} are the same or different, and each are a hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group having optionally a lower alkyl substituent, or combine together with the adjacent nitrogen atom to which they bond to form a 5- to 12-membered saturated heteromonocyclic, heterobicyclic or hetero-sprio ring with or without being intervened with another nitrogen atom or an oxygen atom, said heterocyclic group may optionally have a substituent selected from a lower alkyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkyl group, an amino group having optionally a lower alkyl substituent and a hydroxy-substituted lower alkyl group); (iii) a lower alkoxycarbonyl group; (iv) a hydroxy-substituted lower alkyl group; (v) a pyridyl group being optionally substituted by a lower alkyl group having optionally a halogen substituent on the pyridine ring; (vi) a halogen-substituted lower alkyl group; (vii) a lower alkoxy group; (viii) a cycloalkyl group; (ix) a hydroxy group; (x) a tetrahydropyranyloxy-substituted lower alkyl group; (xi) a pyrimidyl group; (xii) a lower alkoxy-substituted lower alkyl group; (xiii) a carboxyl group; (xiv) a phenyl-lower alkoxy group; (xv) a phenyl-lower alkyl group having optionally a lower alkylenedioxy substituent on the phenyl ring; (xvi) a lower alkanoyloxy group; and (xvii) a piperidinyl group having optionally a lower alkyl substituent on the piperidine ring.

The reaction of the compound (2) and the compound (14), and the reaction of the compound (2) and the compound (15)are carried out under the same conditions as those in the reaction of the compound (2) and the compound (3) or the compound (4) in the above Reaction Scheme-1.

The halogenating reaction of the compound (16) is carried out in the presence of a halogenating agent in a suitable solvent. The halogenating agent may be, for example, halogen molecules (e.g., bromine, chlorine, etc.), iodine chloride, sulfuryl chloride, copper compounds (e.g., copper (II) bromide, etc.), N-halogenated succinimides (e.g., N-bromosuccinimide, N-chlorosuccinimide, etc.). The solvent may be, for example, halogenated hydrocarbons (e.g., dichloromethane, dichloroethane, chloroform, carbon tetrachloride, etc.), fatty acids (e.g., acetic acid, propionic acid, etc.), carbon disulfide, etc. The halogenating agent is usually used in an amount of 1 to 10 moles, preferably in an amount of 1 to 5 moles, to 1 mole of the compound (16). The reaction is usually carried out at 0°C to a boiling point of the solvent to be used, preferably at 0°C to 100°C, for about 5 minutes to 20 hours.

The reaction of the compound (17) and the compound (18) is carried out in a suitable solvent at room temperature to 150°C, preferably at room temperature to about 100°C, for about 1 hour to 10 hours. The solvent may be the same solvents used in the reaction of the carboxylic halide and the amine compound (5) among the reactions between the compound (1b) and the compound (5) in the above Reaction Scheme-2. The compound (18) is used at least in equimolar amount, preferably in an amount of 1 to 1.5 moles, to 1 mole of the compound (17).

In the above process, there is obtained a compound of the formula (21):



(21)

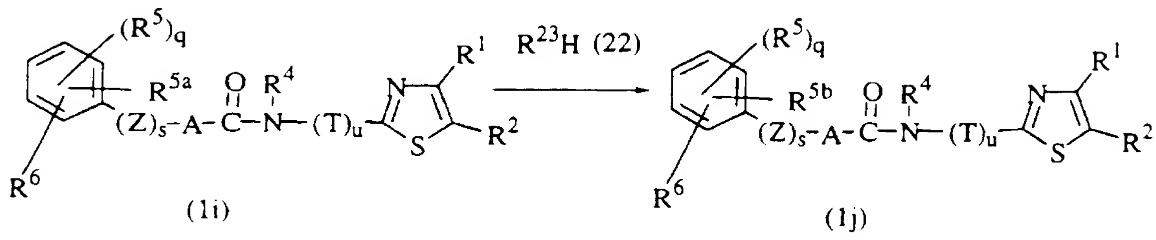
wherein R^1, R^2, R^4, R^5, Z, m, A, R^{21}, s, T, u and X are the same as defined above, which is further treated in the presence of a basic compound in a suitable solvent to give the compound (19). The solvent and the basic compound are the same ones which are used in the reaction of the carboxylic halide and the amine compound (5) in the reaction of the compound (1b) and the compound (5) in the Reaction Scheme-2. The reaction is usually carried out at 0°C to 100°C, preferably at 0°C to about 70°C, for about 1 hour to 5 hours.

The reaction of the compound (19) and the compound (20) is carried out under the same conditions as those in the reaction of the compound (6) and the compound (7) in the above Reaction Scheme-3.

Alternatively, the reaction of the compound (19) and the compound (20) is usually carried out in a suitable solvent at 0°C to 150°C, preferably at room temperature to about 100°C, for about 0.5 hour to 8 hours. The solvent may be any one which does not disturb the reaction, for example, water, alcohols (e.g., methanol, ethanol, isopropanol, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane, diglyme, monoglyme, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), aprotic polar solvents (e.g., N,N-dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide, etc.), etc. The compound (20) is usually used at least in equimolar amount, preferably in an

amount of 1 to 5 moles, to 1 mole of the compound (19). The reaction is promoted when a para-aldehyde is added into the reaction system.

Reaction Scheme-6

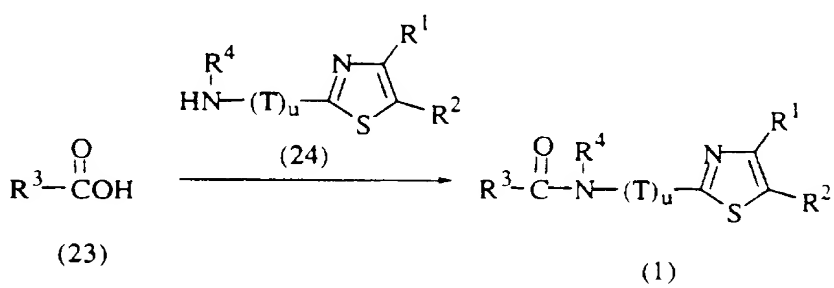


wherein R^1, R^2, R^4, R^5, R^6, Z, s, T, u and A are the same as defined above, q is 1, R^{5a} is a halogen-substituted lower alkyl group, R^{5b} is a group: $-A-NR^7R^8$ (A, R^7, R^8 are the same as defined above) or a lower alkanoyloxy-lower alkyl group, R^{23} is a group: $-NR^7R^8$ (R^7 and R^8 are the same as defined above), or a lower alkanoyloxy group.

The reaction of the compound (1f) and the compound (22) is carried out in the presence or absence of a basic compound in a suitable inert solvent, or without a solvent. The inert solvent includes, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), ethers (e.g., tetrahydrofuran, dioxane, diethylene glycol dimethyl ether, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), lower alcohols (e.g., methanol, ethanol, isopropanol, butanol, tert-butanol, etc.), water, acetic acid, ethyl acetate, acetone, acetonitrile, pyridine, dimethylsulfoxide, dimethylformamide, hexamethylphosphoric triamide, or a mixture of these solvents. The basic compound includes, for example, an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal hydrogen carbonate (e.g.,

sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), sodium hydride, potassium, sodium, sodium amide, an alkali metal alkoxide (e.g., sodium methoxide, etc.), organic basic compounds (e.g., pyridine, N-ethyldiisopropylamine, dimethylaminopyridine, triethylamine, 1,5-diazabicyclo[4.3.0]nonen-5-(DBN), 1,8-diazabicyclo[5.4.0]undecen-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc. The amount of the compound (1i) and the compound (22) is not critical, but the compound (22) is usually used at least in equimolar amount, preferably in an amount of 1 to 10 moles, to 1 mole of the compound (1i). The reaction is usually carried out at 0°C to 200°C, preferably at 0°C to 170°C, for about 30 minutes to 75 hours. Into the reaction system, an alkali metal halide such as sodium iodide, potassium iodide or a copper powder may be added.

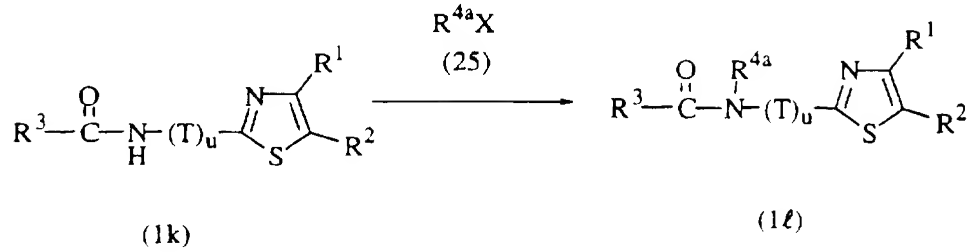
Reaction Scheme-7



wherein R^1, R^2, R^3, R^4, T and u are the same as defined above.

The reaction of the compound (23) and the compound (24) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

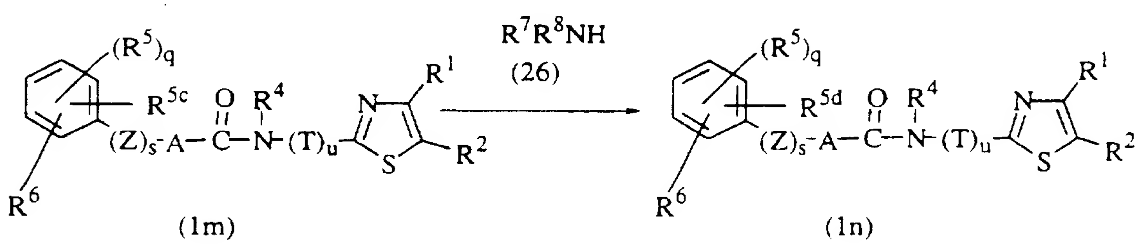
Reaction Scheme-8



wherein R^1, R^2, R^3, T, X and u are the same as defined above, and R^{4a} is a lower alkanoyloxy-lower alkyl group.

The reaction of the compound (1k) and the compound (25) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

Reaction Scheme-9



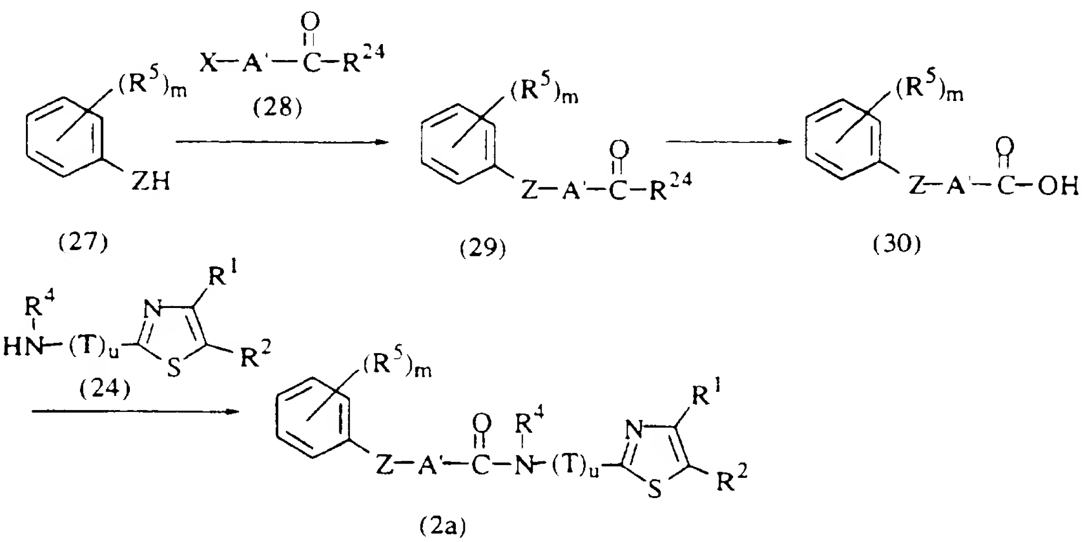
wherein R^1, R^2, R^4, R^5, R^6, R^7, R^8, Z, s, T, u and q are the same as defined above, and R^{5c} is a carboxy-substituted lower alkyl group, R^{5d} is a group: –A–CO–NR^7R^8 (R^7 and R^8 are the same as defined above).

The reaction of the compound (1m) and the compound (26) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

The starting compounds (2), (6) and (23) in the above Reaction Schemes

are prepared by the following processes.

Reaction Scheme-10



wherein R^1, R^2, R^4, R^5, X, Z, T, u and m are the same as defined above, and R^{24} is a hydroxy group, a lower alkoxy group or a phenyl-lower alkoxy group, and A' is a lower alkylene group.

The reaction of the compound (27) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

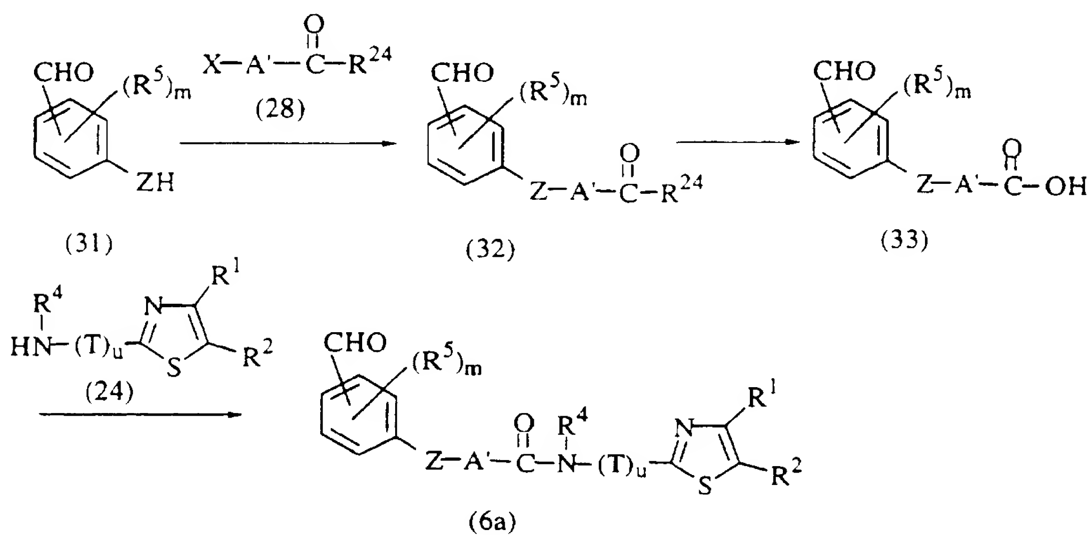
The reaction of converting the compound (29) wherein R^{24} is a lower alkoxy group into the compound (30) is carried out under the same conditions as those in the reaction of converting the compound (1d) into the compound (1e) in the above Reaction Scheme-4.

The reaction of converting the compound (29) wherein R^{24} is a phenyl-lower alkoxy group into the compound (30) is carried out under the same conditions as those in the reaction of converting the compound (5b) into the

compound (5c) in Reaction Scheme-13, which is described hereinbelow.

The reaction of the compound (30) and the compound (24) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

Reaction Scheme-11



wherein R^1, R^2, R^4, R^5, A', Z, R^{24}, T, u and m are the same as defined above.

The reaction of the compound (31) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (27) and the compound (28) in the above Reaction Scheme-10.

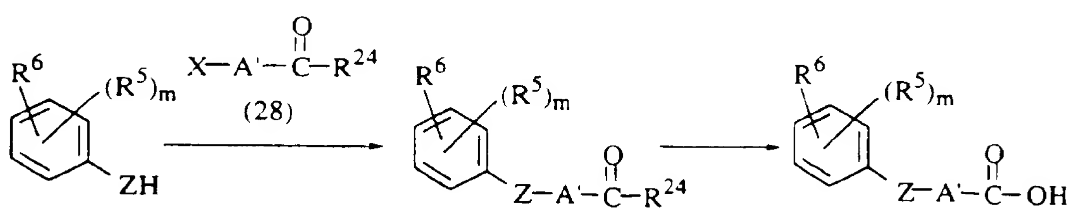
The reaction of converting the compound (32) wherein R^{24} is a lower alkoxy group into the compound (33) is carried out under the same conditions as those in the reaction of converting the compound (29) wherein R^{24} is a lower alkoxy group into the compound (30) in the above Reaction Scheme-10.

The reaction of converting the compound (32) wherein R^{24} is a phenyl-lower alkoxy group into the compound (33) is carried out under the same

conditions as those in the reaction of converting the compound (5b) into the compound (5c) in Reaction Scheme-13, which is described hereinbelow.

The reaction of the compound (33) and the compound (24) is carried out under the same conditions as those in the reaction of the compound (30) and the compound (24) in the above Reaction Scheme-10.

Reaction Scheme-12



(34) (35) (23a)

wherein R^5, R^6, m, A', X, Z and R^{24} are the same as defined above.

The reaction of the compound (34) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (27) and the compound (28) in the above Reaction Scheme-10.

The reaction of converting the compound (35) wherein R^{24} is a lower alkoxy group into the compound (23a) is carried out under the same conditions as those in the reaction of converting the compound (29) wherein R^{24} is a lower alkoxy group into the compound (30) in the above Reaction Scheme-10.

The reaction of converting the compound (35) wherein R^{24} is a phenyl-lower alkoxy group into the compound (23a) is carried out under the same conditions as those in the reaction of converting the compound (5b) into the compound (5c) in Reaction Scheme-13, which is described hereinbelow.

The starting compound (5) is prepared by the following processes.

<u>Reaction Scheme-13</u>

$$\underset{(5a)}{R^{17a}\text{—}R^{25}} \xrightarrow{R^{12}R^{13}NH\ \ (36)} \underset{(5b)}{R^{17b}\text{—}R^{25}} \longrightarrow \underset{(5c)}{R^{17b}H}$$

wherein R^{12}, R^{13} are the same as defined above, R^{17a} is the same groups for R^{17} having at least one oxo group on the heterocyclic group, R^{17b} is the same groups for R^{17} having at least one group: $-N-R^{12}R^{13}$ (R^{12} and R^{13} are the same as defined above) on the heterocyclic group, and R^{25} is a phenyl-lower alkyl group.

The reaction of the compound (5a) and the compound (36) is carried out in the presence of a reducing agent in a suitable solvent or without a solvent. The solvent may be, for example, water, alcohols (e.g., methanol, ethanol, isopropanol, etc.), acetonitrile, formic acid, acetic acid, ethers (e.g., dioxane, diethyl ether, diglyme, tetrahydrorfuran, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), or a mixture of these solvents. The reducing agent may be, for example, formic acid, an alkali metal salt of fatty acid (e.g., sodium formate, etc.), hydrogenating agent (e.g., sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, etc.), catalysts (e.g., palladium-black, palladium-carbon, platinum oxide, platinum black, Raney-nickel, etc.).

When formic acid is used as a reducing agent, the reaction is usually carried out at room temperature to about 200°C, preferably at 50 to 150°C, for one to about 10 hours. The formic acid is used in an excess amount to the amount of the compound (5a).

When a hydrogenating agent is used as a reducing agent, the reaction is

usually carried out at –30°C to about 100°C, preferably at 0°C to 70°C, for 30 minutes to about 12 hours. The hydrogenating agent is used in an amount of 1 to 20 moles, preferably in an amount of 1 to 6 moles, to 1 mole of the compound (5a). Especially, when lithium aluminum hydride is used as a hydrogenating agent, the solvent may be ethers (e.g., diethyl ether, dioxane, tetrahydrofuran, diglyme, etc.), or aromatic hydrogen carbonates (e.g., benzene, toluene, xylene, etc.).

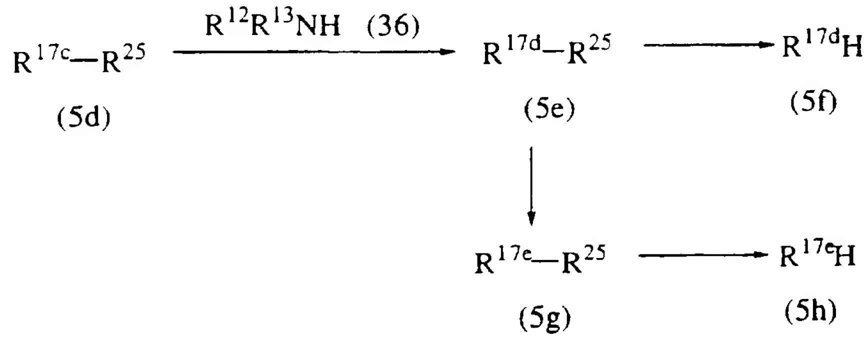
When a catalyst is used as a reducing agent, the reaction is usually carried out under a pressure of atmospheric pressure to 20 atms, preferably under atmospheric pressure to 10 atom of hydrogen gas, in the presence of a hydrogen donor such as formic acid, ammonium formate, cyclohexene, hydrazine hydrate, etc. at a temperature of –30°C to about 100°C, preferably at a temperature of 0°C to 60°C, for about one to 12 hours. The catalyst is used in an amount of 0.1 to 40 % by weight, preferably in an amount of 0.1 to 20 % by weight, to the weight of the compound (5a).

The compound (36) is usually used at least in an equimolar amount, preferably in an amount of 1 to 3 moles, to 1 mole of the compound (5a).

The reaction of converting the compound (5b) into the compound (5c) is carried out by hydrogenation in the presence of a catalyst in a suitable solvent. The solvent may be, for example, water, acetic acid, alcohols (e.g., methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g., hexane, cyclohexane, etc.), ethers (e.g., dioxane, te[illegible] drorfuran, diethyl ether, ethylene glycol dimethyl ether, etc.), esters (e.g., ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g., dimethylformamide, etc.), or a mixture of these solvents. The catalyst may be, for example, palladium. palladium black, palladium hydroxide, palladium hydroxide-

carbon, palladium-carbon, platinum, platinum oxide, copper cromite, Raney nickel, etc. The catalyst is used usually in an amount of 0.02 to 1 time of the amount of the compound (5b). The reaction is usually carried out at a temperature of –20°C to about 100°C, preferably at a temperature of 0°C to about 70°C, under 1 to 10 atms of hydrogen gas, for about 0.5 to about 20 hours.

Reaction Scheme-14



wherein R^{12}, R^{13} and R^{25} are the same as defined above, R^{17c} is the same groups for R^{17} but having at least one carboxyl group on the heterocyclic group, R^{17d} is the same groups for R^{17} but having at least one $-CONR^{12}R^{13}$ (R^{12} and R^{13} are the same as defined above) on the heterocyclic group, and R^{17e} is the same groups for R^{17} but having at least one $-CH_2NR^{12}R^{13}$ (R^{12} and R^{13} are the same as defined above) on the heterocyclic group.

The reaction of the compound (5d) and the compound (36) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

The reactions of converting the compound (5e) into the compound (5f), and converting the compound (5g) into the compound (5h), are carried out

under the same conditions as those in the reaction of converting the compound (5b) into the compound (5c) in the above Reaction Scheme-13.

The reaction of converting the compound (5e) into the compound (5g) is carried out by reduction with using a hydrogenation agent. The hydrogenation agent may be, for example, lithium aluminum hydride, sodium borohydride, diboran, etc., and is used at least in an equimolar amount, preferably in an amount of 1 to 15 moles, to 1 mole of the starting compound. The reduction is carried out in a suitable solvent such as water, a lower alcohol (e.g., methanol, ethanol, isopropanol, etc.), ethers (e.g., tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc.), or a mixture of these solvents. The reaction is usually carried out at a temperature of –60°C top 150°C, preferably at a temperature of –30°C to 100°C, for about 10 minutes to 5 hours. When lithium aluminum hydride or diboran is used as a hydrogenating agent, an anhydrous solvent such as tetrahydrofuran, diethyl ether, diisopropyl ether, diglyme, etc. may be preferably used.

Reaction Scheme-15

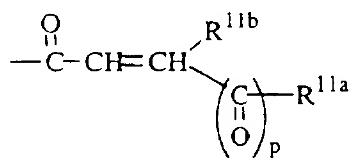
$$\underset{(5i)}{R^{17f}\text{—}R^{25}} \xrightarrow{R^{12}R^{13}NH \quad (36)} \underset{(5j)}{R^{17g}\text{—}R^{25}} \longrightarrow \underset{(5k)}{R^{17g}H}$$

wherein R^{12}, R^{13} and R^{25} are the same as defined above, R^{17f} is the same groups for R^{17} but having at least one halogen-substituted lower alkyl group on the heterocyclic group, and R^{17g} is the same groups for R^{17} but having at least one $-B'-NR^{12}R^{13}$ (B' is a lower alkylene group, R^{12}, R^{13} are the same as defined above) on the heterocyclic group.

The reaction of the compound (5i) and the compound (36) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

The reaction of converting the compound (5j) into the compound (5k) is carried out under the same conditions as those in the reaction of converting the compound (5b) into the compound (5c) in the above Reaction Scheme-13.

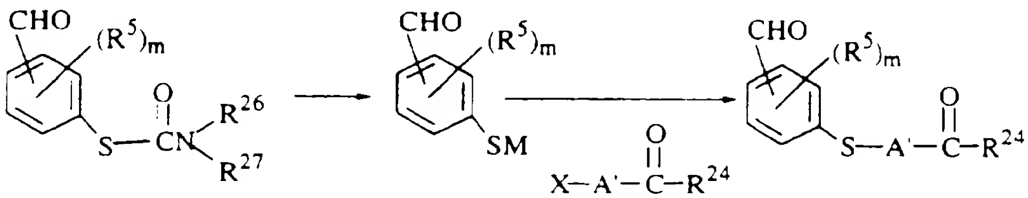
The compound of the formula (1) wherein R^6 is a group of the formula:



wherein R^{11b}, p and R^{11a} are the same as defined above, and showing a trans-configuration at the double bond of the above formula may be isomerized into a cis-compound at the corresponding double bond by being exposed to sunlight, a suitable solvent. The solvent may be the same solvents used in the reaction of the carboxylic halide and the amine compound (5) in the reactions of the compound (1b) and the compound (5) in the above Reaction Scheme-2. The reaction is carried out at a temperature of 0°C to 70°C, preferably at 0°C to room temperature, for about 1 to 10 hours.

Among the starting compounds (32) used in the Reaction Scheme-11, some compounds (32) are prepared by the following process.

Reaction Scheme-16



(37) (38) (28) (32a)

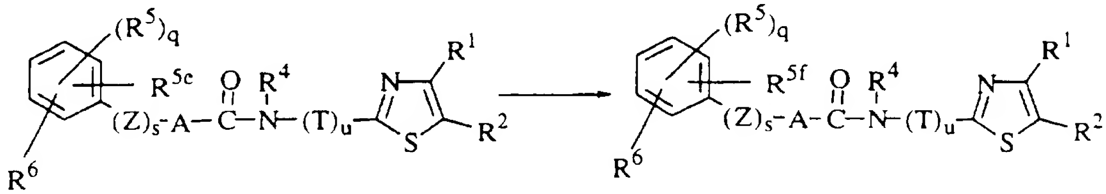
wherein R^5, m, A', M and R^{24} are the same as defined above, and R^{26} and R^{27} are the same or different and each are a lower alkyl group.

The compound of converting the compound (37) into the compound (38) is carried out in the presence of a basic compound in a suitable solvent. The solvent may be, for example, water, lower alcohols (e.g., methanol, ethanol, isopropanol, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), ethers (e.g., dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), or a mixture of these solvents. The basic compound may be, for example, an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), or an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide, etc.), etc. The reaction is usually carried out at room temperature to about 200°C, preferably at room temperature to about 150°C, for about 10 minutes to about 25 hours.

The reaction of the compound (38) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (27) and the compound (28) in the above Reaction Scheme-10.

The each step of the above Reaction Scheme-16 can be carried out in one-pot system without isolating the compound (38) from the reaction system.

Reaction Scheme-17

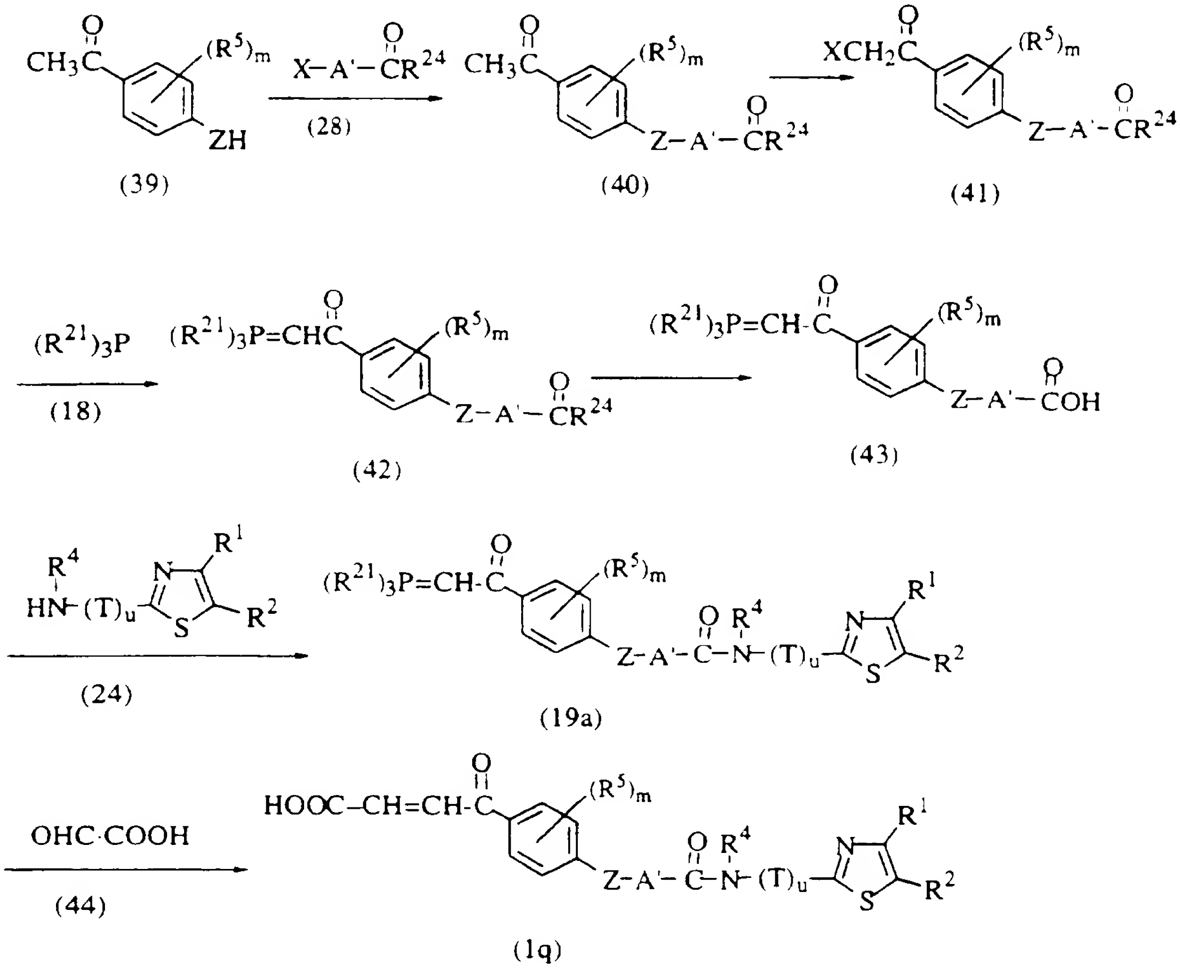


(1o) (1p)

wherein R^1, R^2, R^4, R^5, R^6, s, T, u, q, Z and A are the same as defined above, R^{5e} is a lower alkenyloxy group, and R^{5f} is a hydroxy group.

The reaction of converting the compound (1o) into the compound (1p) is carried out in the presence of a catalyst and an acid in a suitable solvent. The solvent may be, for example, water, acetic acid, alcohols (e.g., methanol, ethanol, isopropanol, etc.), hydrocarbons (e.g., hexane, cyclohexane, etc.), ethers (e.g., dioxane, tetrahydrorfuran, diethyl ether, ethylene glycol dimethyl ether, etc.), esters (e.g., ethyl acetate, methyl acetate, etc.), aprotic polar solvents (e.g., dimethylformamide, etc.), or a mixture of these solvents. The catalyst may be, for example, palladium, palladium black, palladium hydroxide, palladium hydroxide-carbon, palladium-carbon, platinum, platinum oxide, copper cromite, Raney nickel, etc. The acid includes, for example, organic acids such as p-toluene-sulfonic acid, etc. The catalyst is used in an amount of 0.02 to 1 time of the amount of the compound (1o). The acid is usually used in a catalytic amount. The reaction is usually carried out at a temperature of –20°C to about 150°C, preferably at a temperature of 0°C to about 120°C, for about 0.5 to about 20 hours.

Reaction Scheme-18



wherein T, u, R^1, R^2, R^4, A', Z, R^5, m, R^{21}, R^{24} and X are the same as defined above.

The reaction of the compound (39) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

The reaction of converting the compound (40) into the compound (41) is carried out under the same conditions as those in the reaction of converting the compound (16) into the compound (17) in the above Reaction Scheme-5.

The reaction of the compound (41) and the compound (18) is carried out

under the same conditions as those in the reaction of the compound (17) and the compound (18) in the above Reaction Scheme-5.

The reaction of converting the compound (42) wherein R^{24} is a lower alkoxy group into the compound (43) is carried out under the same conditions as those in the reaction of converting the compound (1d) into the compound (1e) in the above Reaction Scheme-4.

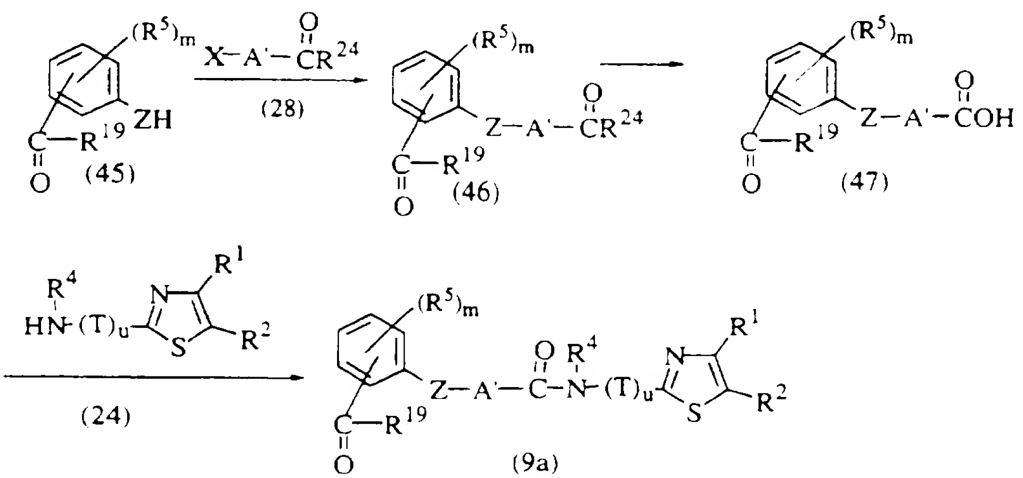
The reaction of converting the compound (42) wherein R^{24} is a phenyl-lower alkoxy group into the compound (43) is carried out under the same conditions as those in the reaction of converting the compound (5b) into the compound (5c) in the above Reaction Scheme-13.

The reaction of the compound (43) and the compound (24) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

The reaction of the compound (19a) and the compound (44) is carried out in a suitable solvent in the presence of a basic compound, at 0°C to 150°C, preferably at room temperature to about 100°C, for about 0.5 to 8 hours. The solvent may be any solvent which does not disturb the reaction, and may be water, alcohols (e.g., methanol, ethanol, isopropanol, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), ethers (e.g., diethyl ether, tetrahydrofuran, dioxane, diglyme, monoglyme, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, etc.), polar solvents (e.g., dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide, etc.), or a mixture of these solvents. The compound (44) is usually used at least in an equimolar amount, preferably in an amount of 1 to 5 moles, to 1 mole of the

compound (19a). The basic compound may be the same basic compounds which are used in the reaction of the compound (6) and the compound (7) in the above Reaction Scheme-3. The starting compound (9) can be prepared, for example, by the process in Reaction Scheme-19 or -20, as explained below.

Reaction Scheme-19



wherein T, u, R^1, R^2, R^4, A', Z, R^5, m, X, R^{24} and R^{19} are the same as defined above.

The reaction of the compound (45) and the compound (28) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

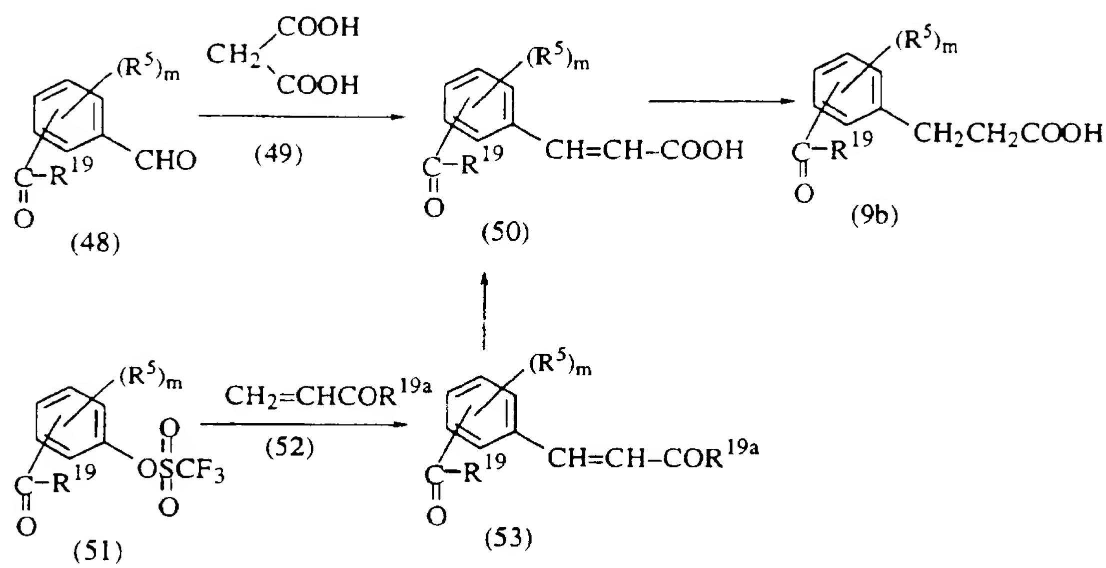
The reaction of converting the compound (46) wherein R^{24} is a lower alkoxy group into the compound (47) is carried out under the same conditions as those in the reaction of converting the compound (1d) into the compound (1e) in the above Reaction Scheme-4.

The reaction of converting the compound (46) wherein R^{24} is a phenyl-lower alkoxy group into the compound (47) is carried out under the same

conditions as those in the reaction of converting the compound (5b) into the compound (5c) in the above Reaction Scheme-13.

The reaction of the compound (47) and the compound (24) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2.

Reaction Scheme-20



wherein R^{19}, R^5 and m are the same as defined above, R^{19a} is a lower alkoxy group.

The reaction of the compound (48) and the compound (49) is carried out in a suitable solvent in the presence of a basic compound. The solvents and the basic compounds are the same ones which are used in the reaction of the compound (6) and the compound (7) in the above Reaction Scheme-3. The compound (49) is usually used at least in an equimolar amount, preferably in an amount of 1 to 3 moles, to 1 mole of the compound (48). The reaction is usually carried out at room temperature to 200°C, preferably at room temperature to

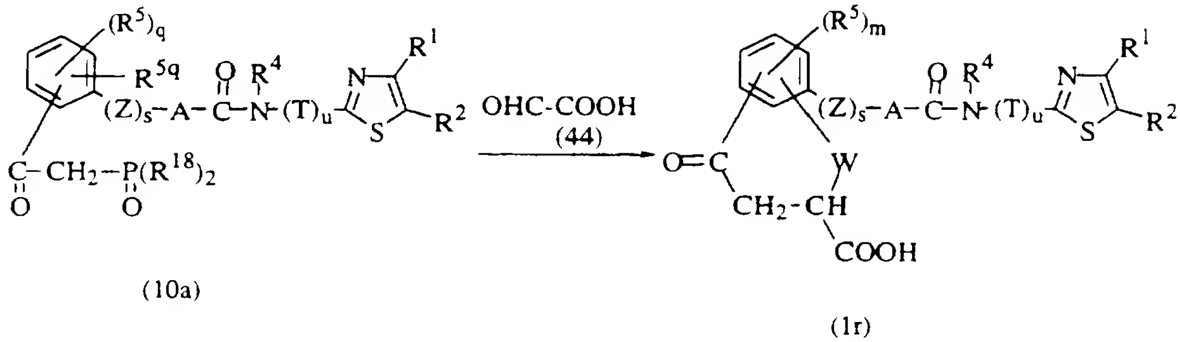
about 150°C, for about 1 to about 60 hours.

The reaction of converting the compound (50) into the compound (9b) is carried out under the same conditions as those in the reaction of converting the compound (5b) into the compound (5c) in the above Reaction Scheme-13.

The reaction of the compound (51) and the compound (52) is carried out in a suitable solvent in the presence of a basic compound and a catalyst. The solvent includes, for example, ethers (e.g., diethyl ether, tetrahydrofuran, dioxane, monoglyme, diglyme, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), aliphatic hydrocarbons (e.g., n-hexane, heptane, cyclohexane, etc.), dimethylformamide, dimethylsulfoxide, hexamethylphosphoric triamide, or a mixture of these solvents. The basic compound may be the same ones which are used in the reaction of the compound (1b) and the compound (5) using a carboxylic halide in the above Reaction Scheme-2. The catalyst includes, for example, palladium chloride, tetrakis(triphenylphosphine)palladium, palladium acetate, 1,3-bis(diphenylphosphino)propane, or a mixture of these solvents. The reaction is usually carried out at 0°C to 200°C, preferably at room temperature to about 150°C, for about 1 to about 20 hours. The compound (52) is usually used at least in an equimolar amount, preferably in an amount of 1 to 10 moles, to 1 mole of the compound (51), The basic compound is usually used at least in an equimolar amount, preferably in an amount of 1 to 3 moles, to 1 mole of the compound (51). The catalyst is used at least in an excess amount of the compound (51).

The reaction of converting the compound (53) into the compound (50) is carried out under the same conditions as those in the reaction of converting the compound (1d) into the compound (1e) in the above Reaction Scheme-4.

Reaction Scheme-21

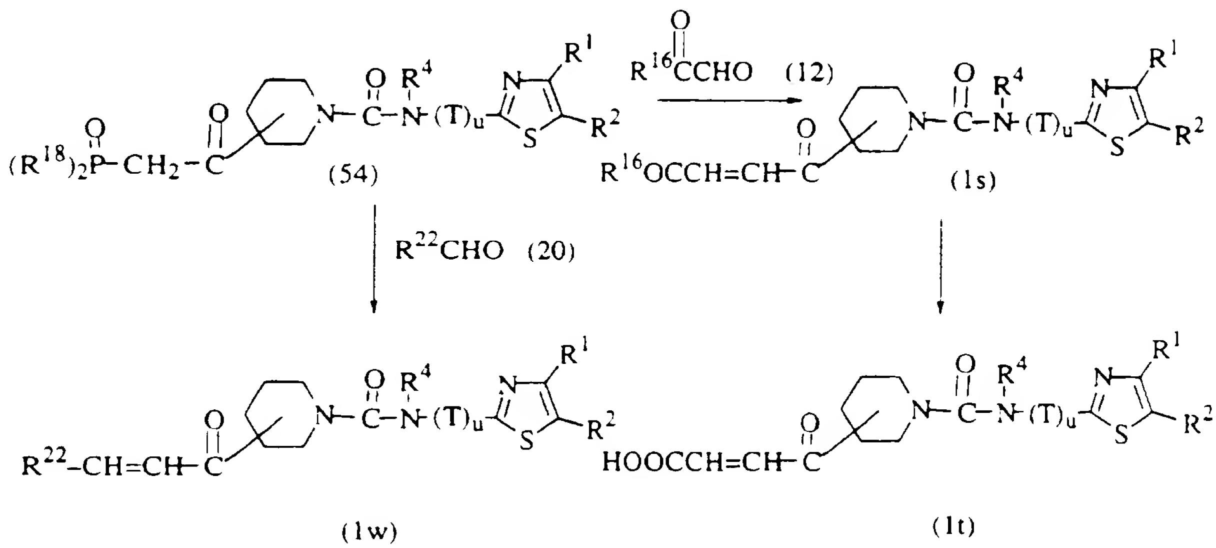


wherein T, u, R^5, q, R^{18}, R^1, R^2, R^4, A, Z, s and W are the same as defined above, R^{5q} is an amino group having optionally a lower alkyl substituent, and a group: $-C(O)CH_2-P(O)(R^{18})_2$ and a group: $-R^{5q}$ are positioned each other at ortho-position.

The reaction of the compound (10a) and the compound (44) is carried out under the same conditions as those in the reaction of the compound (10) and the compound (12) in the above Reaction Scheme-3.

The compound (1r) wherein W is a group of the formula: $-\overset{+}{N}{<}^{R^{29b}}_{R^{29b}}\ X^-$ wherein R^{29b} and X^- are the same as defined above) can be obtained by treating with a hydrohalogenic acid such as hydrochloric acid, hydrobromic acid, etc., after the reaction is complete.

Reaction Scheme-22



wherein R^1, R^2, T, u, R^4 R^{16}, R^{18} and R^{22} are the same as defined above.

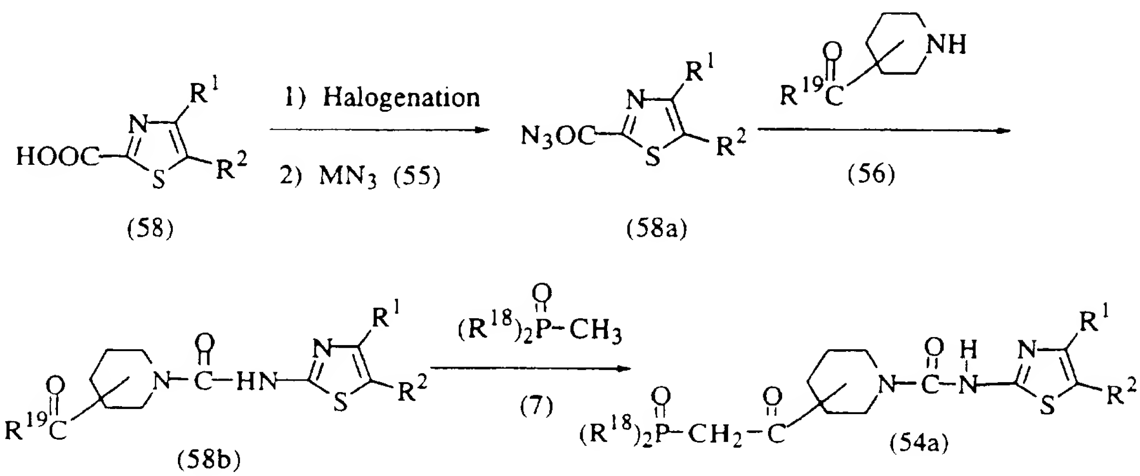
The reaction of the compound (54) and the compound (12) is carried out under the same conditions as those in the reaction of the compound (10) and the compound (12) in the above Reaction Scheme-3.

The reaction of converting the compound (1s) wherein R^{16} is a lower alkoxy group into the compound (1t) is carried out under the same conditions as those in the reaction of converting the compound (1d) into the compound (1e) in the above Reaction Scheme-4.

The reaction of the compound (54) and the compound (20) is carried out under the same conditions as those in the reaction of the compound (10) and the compound (20) in the above Reaction Scheme-3.

The starting compound (54) is prepared, for example, by the following process.

Reaction Scheme-23



wherein R^1, R^2, M, R^{19} and R^{18} are the same as defined above.

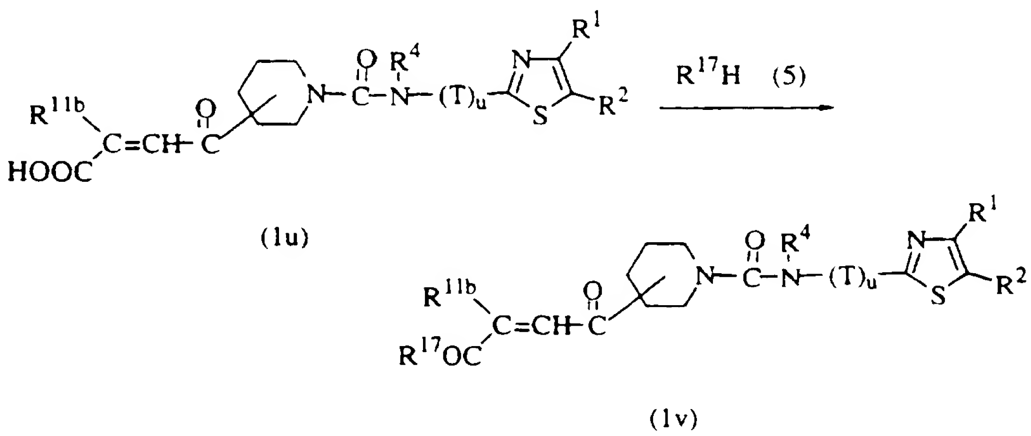
The halogenation reaction of the compound (58) is carried out under conventional halogenation conditions which are employed in the halogenation reaction of a carboxylic acid. The reaction of the carboxylic acid halide compound of the compound (58) and the compound (55) is carried out in the presence or absence of a basic compound in a suitable solvent. The solvent includes, for example, halogenated hydrocarbons (e.g., methylene chloride, chloroform, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), ethers (e.g., diethyl ether, tetrahydrofuran, dimethoxyethane, etc.), esters (e.g., methyl acetate, ethyl acetate, etc.), aprotic polar solvents (e.g., N,N-dimethyl-formamide, dimethylsulfoxide, hexamethylphosphoric triamide, etc.), alcohols (e.g., methanol, ethanol, propanol, butanol, 3-methoxy-1-butanol, ethyl-cellosolve, methylcellosolve, et.), pyridine, acetone, acetonitrile, water, or a mixture of these solvents. The basic compound includes, for example, organic basic compounds such as triethylamine, trimethylamine, pyridine, dimethyl-aniline, N-methylmorpholine, DBN, DBU, DABCO, etc., or inorganic basic

compounds such as potassium carbonate, sodium carbonate, potassium hydride, sodium hydride, potassium hydroxide, sodium hydroxide, silver carbonate, sodium methoxide, sodium ethoxide, etc. The compound (55) is used at least in an equimolar amount, preferably in an amount of 1 to 3 moles, to 1 mole of the carboxylic acid halide compound of the compound (58). The reaction is usually carried out at –30°C to about 180°C, preferably at 0°C to about 150°C, for about 5 minutes to about 30 hours.

The reaction of the compound (58a) and the compound (56) is carried out in a suitable solvent, or without a solvent, at 0°C to about 200°C, preferably at room temperature to about 150°C. The solvent may be the same solvents used in the above reaction of the carboxylic halide of the compound (58) and the compound (55). The compound (56) is used at least in an equimolar amount, preferably in an amount of 1 to 1.5 mole, to 1 mole of the compound (58a). The reaction is carried out for about 1 hour to about 5 hours.

The reaction of the compound (58b) and the compound (7) is carried out under the same conditions as those in the reaction of the compound (9) and the compound (7) in the above Reaction Scheme-3. '

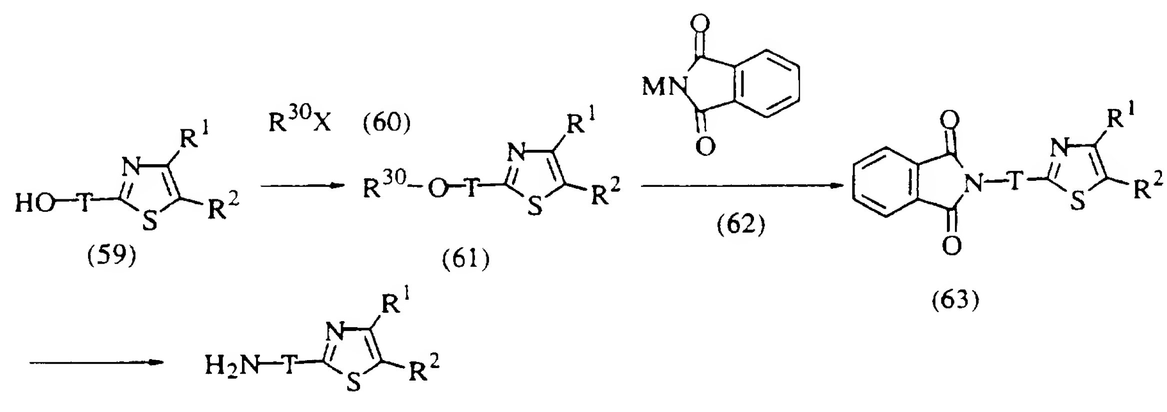
Reaction Scheme-24



wherein R^1, R^2, R^4, R^{11b}, T, u and R^{17} are the same as defined above.

The reaction of the compound (1u) and the compound (5) is carried out under the same conditions as those in the reaction of the compound (1b) and the compound (5) in the above Reaction Scheme-2. The starting compound (24) can be prepared, for example, by the method of Reaction Scheme-25, as explained below.

Reaction Scheme-25



(24a)

wherein R^1, R^2, M, X and T are the same as defined above, and R^{30} is a lower alkylsulfonyl group.

The reaction of the compound (59) and the compound (60) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6. The reaction of the compound (61) and the compound (62) is carried out under the same conditions as those in the reaction of the compound (1i) and the compound (22) in the above Reaction Scheme-6.

The reaction of converting the compound (63) into the compound (24a) is carried out by treating the compound (63) with hydrazine in a suitable

solvent, or hydrolyzing the compound (63). The solvent used in the reaction with hydrazine may be, in addition to water, the same solvents used in the reaction using a carboxylic acid halide in the reaction of the compound (1b) and the compound (5) in Reaction Scheme-2. The reaction is usually carried out at room temperature to about 120°C, preferably at 0°C to about 100°C, for about 0.5 hour to about 5 hours. The hydrazine is usually used at least in an equimolar amount, preferably in an amount of 1 to 6 moles, to 1 mole of the compound (63).

The hydrolysis is carried out in a suitable solvent or without a solvent in the presence of an acid or a basic compound. The solvent includes, for example, water, lower alcohols (e.g., methanol, ethanol, isopropanol, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), ethers (e.g., diethyl ether, dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, etc.), fatty acids (e.g., acetic acid, formic acid, etc.), or a mixture of these solvents. The acid includes, for example, mineral acids (e.g., hydrochloric acid, hydrobromic acid, etc.), organic acids (e.g., formic acid, acetic acid, aromatic sulfonic acids, etc.). The basic compound includes, for example, an alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), an alkali metal or alkaline earth metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, calcium hydroxide, etc.). The reaction is usually carried out at room temperature to about 200°C, preferably at room temperature to abo' 150°C, for about 10 minutes to about 25 hours.

Among the red compounds (1) of the present invention, the compounds having an acidic group can easily be converted into salts by treating them with a pharmaceutically acceptable basic compound. The basic compound includes, for example, an alkali metal hydroxide such as sodium

hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, etc., an alkali metal carbonate such as sodium carbonate, etc., an alkali metal hydrogen carbonate such as potassium hydrogen carbonate, an alkali metal alkoxide such as sodium methylate, potassium ethylate, and the like.

Besides, among the desired compounds (1) of the present invention, the compounds having a basic group can easily be converted into acid addition salts thereof by treating them with a pharmaceutically acceptable acid. The acid includes, for example, inorganic acids (e.g. sulfuric acid, nitric acid, hydrochloric acid, hydrobromic acid, etc.), and organic acids (e.g. acetic acid, p-toluenesulfonic acid, ethanesulfonic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, benzoic acid, etc.). These salts can be also used as an active ingredient of the pharmaceutical composition of the present invention as well as the compound (1) in a free form. In addition, the compounds of the present invention also include stereoisomers and optical isomers, and these isomers are also used as an active ingredient.

The desired compound obtained in the above Reaction Schemes can easily be isolated and purified by conventional isolation methods from the reaction system. The isolation methods are, for example, distillation method, recrystallization method, column chromatography, ion exchange chromatography, gel chromatography, affinity chromatography, preparative thin layer chromatography, extraction with solvent, dilution method, and the like.

The compounds (1) of the present invention are useful as a protein kinase inhibitor, and can be used in the form of a conventional pharmaceutical preparation. The preparation is prepared by using conventional diluents or carriers such as fillers, thickening agents, binders, wetting agent, disintegrators,

surfactants, lubricants, and the like. The pharmaceutical preparations can be selected from various forms in accordance with the desired utilities, and the representative forms are tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.), and the like. In order to form in tablets, there are used carriers such as vehicles (e.g. lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, etc.), binders (e.g. water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, etc.), disintegrators (e.g. dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, etc.), disintegration inhibitors (e.g. white sugar, stearin, cacao butter, hydrogenated oils, etc.), absorption promoters (e.g. quaternary ammonium base, sodium laurylsulfate, etc.), wetting agents (e.g. glycerin, starches, etc.), adsorbents (e.g. starches, lactose, kaolin, bentonite, colloidal silicates, etc.), lubricants (e.g. purified talc, stearates, boric acid powder, polyethylene glycol, etc.), and the like. Moreover, the tablets may also be in the form of a conventional coated tablet, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film coating tablets, or double or multiple layer tablets. In the preparation of pills, the carriers may be conventional ones, and include, for example, vehicles (e.g. glucose, lactose, starches, cacao butter, hydrogenated vegetable oils, kaolin, talc, etc.), binders (e.g. gum arabic powder, tragacanth powder, gelatin, ethanol, etc.), disintegrators (e.g. laminaran, agar, etc.), and the like. In the preparation of suppositories, the carriers may be

conventional ones, and include, for example, polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters, gelatin, semi-synthetic glycerides, and the like. The capsules are prepared by mixing the active compound with a conventional carrier, and fulfilling the mixture into hard gelatin capsules or soft capsules. In the preparation of injections, the solutions and suspensions are sterilized and are preferably made isotonic with the blood. In the preparation of these solutions, emulsions and suspensions, there are used conventional diluents, such as water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if required.

The amount of the desired compound (1) of the present invention or a salt thereof to be incorporated into the pharmaceutical preparation is not specified but may be selected from a broad range, but usually, it is preferably in the range of about 1 to 70 % by weight, preferably in the range of about 5 to 50 % by weight.

The pharmaceutical preparation of the present invention may be administered in any method, and the suitable method for administration may be determined in accordance with various forms of preparations, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like.

For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are administered in intrarectal route.

The dosage of the pharmaceutical preparation of the present invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but it is usually in the range of about 0.6 to 50 mg of the compound (1) or a salt thereof per 1 kg of body weight of the patient per day. The active compound is contained in an amount of about 10 to 1000 mg per one unit of the dosage form.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail by the following Preparations of pharmaceutical composition, Reference Examples of processes for preparing the starting compounds to be used for preparing the desired compounds of the present invention, and Examples of processes for preparing the desired compounds, and Experiment of the activities of the desired compounds of the present invention.

Preparation 1

Film coated tablets are prepared from the following components.

Components	Amount
2-[2-Methoxy-4-{3-[4-(4-methyl-1-piperazinyl)-1-piperidinylcarbonyl]acryloyl}phenoxymethyl-carbonylamino]benzothiazole	150 g
Avicel (trade mark of microcrystalline cellulose manufactured by Asahi Chemical Industry, Co., Ltd.)	40 g
Corn starch	30 g
Magnesium stearate	2 g
Hydroxypropyl methylcellulose	10 g
Polyethylene glycol-6000	3 g
Castor oil	40 g
Ethanol	40 g

The active compound of the present invention, Avicel, corn starch and magnesium stearate are mixed and kneaded, and the mixture is tabletted by using a conventional pounder (R 10 mm) for sugar coating. The tablets thus obtained are coated with a film coating agent consisting of hydroxypropyl

methylcellulose, polyethylene glycol-6000, castor oil and ethanol to give film coated tablets.

Preparation 2

Tablets are prepared from the following components.

Components	Amount
2-[3-Methoxy-4-{3-[4-(3,4-dimethyl-1-piperazinyl)-1-piperidinylcarbonyl]acryloyl}phenoxymethyl-carbonylamino]benzimidazole	150 g
Citric acid	1.0 g
Lactose	33.5 g
Dicalcium phosphate	70.0 g
Pullonic F-68	30.0 g
Sodium laurylsulfate	15.0 g
Polyvinylpyrrolidone	15.0 g
Polyethylene glycol (Carbowax 1500)	4.5 g
Polyethylene glycol (Carbowax 6000)	45.0 g
Corn starch	30.0 g
Dry sodium stearate	3.0 g
Dry magnesium stearate	3.0 g
Ethanol	q.s.

The active compound of the present invention, citric acid, lactose, dicalcium phosphate, Pullonic F-68 and sodium laurylsulfate are mixed.

The mixture is screened with No. 60 screen and is granulated with an alcohol solution containing polyvinylpyrrolidone, Carbowax 1500 and 6000. If required, an alcohol is added thereto so that the powder mixture is made a paste-

like mass. Corn starch is added to the mixture and the mixture is continuously mixed to form uniform particles. The resulting particles are passed through No. 10 screen and entered into a tray and then dried in an oven at 100°C for 12 to 14 hours. The dried particles are screened with No. 16 screen and thereto are added dry sodium laurylsulfate and dry magnesium stearate, and the mixture is tabletted to form the desired shape.

The core tablets thus prepared are vanished and dusted with talc in order to guard from wetting. Undercoating is applied to the core tablets. In order to administer the tablets orally, the core tablets are vanished several times. In order to give round shape and smooth surface to the tablets, further undercoating and coating with lubricant are applied thereto. The tablets are further coated with a coloring coating material until the desired colored tablets are obtained. After drying, the coated tablets are polished to obtain the desired tablets having uniform gloss.

Preparation 3

An injection preparation is prepared from the following components.

Components	Amount
2-{2-(3-Morpholinopropyl)-4-[3-(4-pyridyl)acryloyl}-phenoxymethylcarbonylamino}benzothiazole	5 g
Polyethylene glycol (molecular weight: 4000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl-paraben	0.18 g
Propyl-paraben	0.02 g

Distilled water for injection 10.0 ml

The above parabens, sodium metabisulfite and sodium chloride are dissolved with stirring in distilled water of half volume of the above at 80°C. The solution thus obtained is cooled to 40°C, and the active compound of the present invention and further polyethylene glycol and polyoxyethylene sorbitan monooleate are dissolved in the above solution. To the solution is added distilled water for injection to adjust to the desired volume, and the solution is sterilized by filtering with an appropriate filter paper to give an injection preparation.

Reference Example 1

A solution of o-isopropylphenol (39.5 g), potassium carbonate (40 g) and ethyl α-bromoacetate (40 ml) in dimethylformamide (300 ml) is heated with stirring at 80°C for 8 hours. To the mixture is added water, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and concentrated under reduced pressure to remove the solvent. The residue thus obtained is dissolved in a solution of sodium hydroxide (20 g) in water (300 ml) and ethanol (200 ml), and the mixture is refluxed for 1.5 hour. After cooling, the mixture is acidified with conc. hydrochloric acid, and the precipitated crystals are collected by filtration to give α-(2-isopropylphenoxy)acetic acid (37 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 1.24 (6H, d, J=7Hz), 3.39 (1H, sept, J=7Hz), 4.69 (2H, s), 6.75 (1H, dd, J=1Hz, J=8Hz), 6.95-7.3 (3H, m)

Reference Example 2

A solution of α-(2-isopropylphenoxy)acetic acid (13.1 g) in thionyl

chloride (30 ml) is refluxed for 30 minutes. The mixture is concentrated under reduce pressure to remove the excess thionyl chloride, and the resultant is dissolved in dichloromethane (50 ml). The mixture is added dropwise into a solution of 2-aminobenzothiazole (9.1 g) and pyridine (7.2 ml) in dichloromethane (100 ml) under ice-cooling. The mixture is stirred at the same temperature for five hours, and then washed with water, dried, and concentrated under reduced pressure. To the residue is added ethanol to give 2-(2-isopropylphenoxymethylcarbonylamino)benzothiazole (16.66 g).

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 1.32 (6H, d, J=7Hz) 3.43 (1H, sept, J=7Hz), 4.78 (2H, s), 6.85 (1H, dd, J=1Hz, J=8Hz), 7.0-7.55 (5H, m), 7.8-7.9 (2H, m), 9.74 (1H, br)

Reference Example 3

To a solution of dimethyl methylphosphonate (19.5 ml) in anhydrous tetrahydrofuran (300 ml) is added a 1.72 M solution of n-butyl lithium in n-hexane (107 ml) at –50°C. Thirty minutes later, to the mixture is added in portions 2-(2-methoxy-4-formylphenoxymethylcarbonylamino)benzothiazole (20.5 g) under nitrogen atmosphere. The mixture is stirred at –50°C for one hour, and thereto is added water. The mixture is acidified with conc. hydrochloric acid, and extracted with ethyl acetate. The extract is washed with water, dried and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; dichloromethane:methanol = 200:1 → 30:1) to give dimethyl {2-[3-methoxy-4-(2-benzothiazolylaminocarbonylmethoxy)phenyl]-2-hydroxyethyl}phosphonate (19.0 g).

^{1}H-NMR ($CDCl_3$) δppm: 2.05-2.35 (2H, m), 3.73, 3.76, 3.78 and 3.81 (6H, each s), 3.98 (2H, d, J=2.5Hz), 4.01 (3H, s), 4.77 (2H, s), 5.0-5.15 (1H, m), 6.90 (1H, dd, J=2Hz, J=8Hz), 6.98 (1H, d, J=8Hz), 7.07 (1H, d, J=2Hz), 7.25-7.5 (2H, m), 7.8-7.9 (2H, m), 10.66 (1H, br)

To a solution of dimethyl {2-[3-methoxy-4-(2-benzothiazolylamino-carbonylmethoxy)phenyl]-2-hydroxyethyl}phosphonate (19.0 g) in chloroform (300 ml) is added active manganese dioxide (17.7 g), and the mixture is refluxed for three hours. To the mixture is additionally added active manganese dioxide (18 g), and the mixture is refluxed for three hours. To the mixture is further added active manganese dioxide (20 g), and the mixture is refluxed for three hours. The manganese dioxide is collected by filtration, and washed with chloroform. The filtrate and the washings are combined and concentrated under reduced pressure to remove the chloroform. The residue is purified by silica gel column chromatography (solvent; dichloromethane:methanol = 200:1 → 50:1) to give dimethyl {[3-methoxy-4-(2-benzothiazolylaminocarbonylmethoxy)-benzoyl]methyl}phosphonate (7.76 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 3.62 (2H, d, J=22.5Hz), 3.79 (6H, d, J=11.2Hz), 4.04 (3H, s), 4.85 (2H, s), 7.02 (1H, d, J=8.5Hz), 7.3-7.55 (2H, m), 7.6-7.7 (2H, m), 7.8-7.9 (2H, m), 10.31 (1H, br)

Reference Example 4

To a solution of chloroacetyl chloride (10.0 ml) in anhydrous 1,2-dichloro-ethane (250 ml) is added aluminum chloride (12 g) at room temperature, and the mixture is stirred for 20 minutes. To the mixture is added at once 2-(2-isopropyl-

phenoxymethylcarbonylamino)benzothiazole (20 g), and the mixture is stirred at room temperature for one hour. The reaction mixture is poured into water, and thereto is added n-hexane. The precipitates are collected by filtration, washed with water, and dried to give 2-[2-isopropyl-4-(2-chloroacetyl)phenoxymethylcarbonylamino]benzothiazole (25.9 g).

White powder

^{1}H-NMR (DMSO-d_6) δppm: 1.24 (6H, d, J=7Hz), 3.38 (1H, m), 5.12 (4H, s), 7.01 (1H, d, J=9Hz), 7.25-7.55 (2H, m), 7.7-7.95 (3H, m), 7.97 (1H, d, J=8Hz), 13.00 (1H, br)

Reference Example 5

A suspension of 2-[2-isopropyl-4-(2-chloroacetyl)phenoxymethylcarbonylamino]benzimidazole (4.0 g) and triphenylphosphine (2.8 g) in chloroform (100 ml) is refluxed for 7 hours. The reaction mixture is concentrated under reduced pressure, and the residue is crystallized from dichloromethane-diethyl ether to give [3-isopropyl-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]methyltriphenylphosphonium chloride (3.8 g).

^{1}H-NMR (DMSO-d_6) δppm: 1.23 (6H, d, J=7Hz), 3.40 (1H, m), 5.18 (2H, s), 6.19 (2H, d, J=13.5Hz), 7.09 (1H, d, J=9Hz), 7.25-7.5 (2H, m), 7.6-8.05 (19H, m), 12.77 (1H, s)

To a solution of [3-isopropyl-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]methyltriphenylphosphonium chloride (3.3 g) in methanol (50 ml) is added DBU (1 ml), and the mixture is stirred at room temperature for two hours. The precipitated crystals are collected by filtration, washed with methanol, and dried to give [3-isopropyl-4-(2-benzothiazolylaminocarbonyl-

methoxy)benzoyl]methylenetriphenylphosphorane (2.27 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 1.32 (6H, d, J=7Hz), 3.42 (1H, sept, J=7Hz), 4.2-4.6 (1H, m), 4.73 (2H, s), 6.75 (1H, d, =8.5Hz), 7.25-8.0 (21H, m), 10.01 (1H, br)

Using the suitable starting compounds, the following compound is obtained in the same manner as in Reference Example 5.

[3-(3-chloropropyl)-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]-methylenetriphenylphosphonium chloride:

White powder

^{1}H-NMR ($CDCl_3$) δppm: 2.11 (2H, tt, J=6.6Hz, J=8.0Hz), 2.86 (2H, t, J=8.0Hz), 3.71 (2H, t, J=6.6Hz), 5.20 (2H, s), 6.17 (2H, d, J=12.8Hz), 7.13 (1H, d, J=8.7Hz), 7.34 (1H, t, J=7.5Hz), 7.48 (1H, t, J=7.0 Hz), 7.76-8.02 (19H, m), 12.75 (1H, br)

Reference Example 6

To dimethylformamide (200 ml) are added 2-methoxy-4-acetylphenol (20 g), ethyl α-bromoacetate (15 ml) and potassium carbonate (18.3 g), and the mixture is stirred at room temperature overnight. After the reaction is complete, water is added to the mixture, and the mixture is extracted with ethyl acetate. The extract is washed with aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate, and concentrated under reduced pressure to remove the solvent. The resulting crystals are collected, and washed with n-hexane-diethyl ether to give ethyl α-(2-methoxy-4-acetylphenoxy)acetate (23.86 g).

To chloroform (230 ml) are added ethyl α-(2-methoxy-4-acetylphenoxy)-

acetate (23 g) and copper (II) bromide (55 g), and the mixture is refluxed for 3.5 hours. After the reaction is complete, the mixture is filtered through a cerite pad to remove the precipitates, and washed with sodium hypochlorite. The filtrate is dried over magnesium sulfate, and concentrated under reduced pressure to remove the solvent, and then crystallized to give ethyl α-[2-methoxy-4-(2-bromoacetyl)phenoxy]acetate (21.28 g).

To chloroform (200 ml) are added ethyl α-[2-methoxy-4-(2-bromoacetyl)-phenoxy]acetate (20 g) and triphenylphosphine (20.6 g) in an ice-bath, and the mixture is stirred for one hour. After confirming that the starting compounds are well consumed, the mixture is washed with an aqueous potassium carbonate solution. The mixture is dried over magnesium sulfate, and concentrated under reduced pressure to remove the solvent. To the residue is added methanol (200 ml), and thereto is added dropwise sodium hydroxide in an ice-bath. After confirming that the starting compounds are well consumed, to the mixture is added conc. hydrochloric acid. The precipitated crystals are washed with water and diethyl ether, and dried to give (3-methoxy-4-carboxymethoxybenzoyl)-methylenetriphenylphosphorane (25 g).

To dichloromethane (50 ml) are added (3-methoxy-4-carboxymethoxy-benzoyl)methylenetriphenylphosphorane (5 g), 2-aminobenzothiazole (1.9 g), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.93 g) and triethylamine (3.3 ml), and the mixture is stirred overnight. After the reaction is complete, the mixture is washed with an aqueous sodium hydrogen carbonate solution, and dried over magnesium sulfate to remove the solvent, and further recrystallized from toluene to give [3-methoxy-4-(2-benzothiazolylaminocarbonylmethoxy)-benzoyl]methylenetriphenylphosphorane (5.17 g).

Pale yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 4.03 (3H, s), 4.12-4.62 (1H, m), 4.79 (2H, s), 6.96 (1H, d, J=8.3Hz), 7.25-7.90 (22H, m)

Reference Example 7

To a solution of N-benzyl-4-piperidone (8.0 g) and 3,4-dimethyl-piperazine (9.5 g) in ethanol (100 ml) are added 5 % platinum-carbon (2 g) and acetic acid (14.4 ml), and the mixture is subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. Water is added to the resultant, and the mixture is basified with a 5% aqueous sodium hydroxide solution, and the mixture is extracted with diethyl ether. The extract is washed with water, dried and concentrated under reduced pressure to remove the solvent. The residue is dissolved in ethanol, and thereto is added to conc. hydrochloric acid to give a hydrochloride. The resulting white powder is collected by filtration, dissolved in water, and basified with a 5% aqueous sodium hydroxide solution. The mixture is extracted with diethyl ether, washed with water, dried, and concentrated under reduced pressure to give 4-(3,4-dimethyl-1-piperazinyl)-1-benzylpiperidine (4.2 g).

^{1}H-NMR ($CDCl_3$) δppm: 1.04 (3H, d, J=6Hz), 1.45-2.5 (12H, m), 2.27 (3H, s), 2.7-3.05 (4H, m), 3.48 (2H, s), 7.31 (5H, m)

To a solution of 4-(3,4-dimethyl-1-piperazinyl)-1-benzylpiperidine (4.2 g) in ethanol (50 ml) is added 20 % palladium hydroxide-carbon (0.4 g), and the mixture is subjected to catalytic hydrogenation at 50°C under atmospheric pressure. The catalyst is removed by filtration, and the filtrate is concentrated

under reduced pressure. The residue is evaporated to give 4-(3,4-dimethyl-1-piperazinyl)piperidine (1.65 g).

Colorless oil

b.p. 145°C (0.3 mmHg)

^{1}H-NMR ($CDCl_3$) δppm: 1.05 (3H, d, J=6Hz), 1.25-1.55 (2H, m), 1.75-3.3 (14H, m), 2.31 (3H, s)

Reference Example 8

A solution of 1-benzyl-L-proline (50 g) in dichloromethane (300 ml) is cooled with ice. To the solution is added N-methylmorpholine (22.5 g), and then further thereto is added dropwise isobutyl chloroformate (30 g). The mixture is stirred at the same temperature for about one hour, and thereto is added dropwise pyrrolidine (18.8 ml) at the same temperature. The mixture is warmed to room temperature, and stirred for two days. The mixture is washed twice with water (250 ml), and dried over magnesium sulfate. The mixture is concentrated under reduced pressure, and the residue is recrystallized from ethyl acetate-n-hexane to give 2-(1-pyrrolidinyl)carbonyl-1-benzylpyrrolidine (31 g), as white powder.

In ethanol (300 ml) is suspended 5 % palladium-carbon (3 g), and thereto is added 2-(1-pyrrolidinyl)carbonyl-1-benzylpyrrolidine (30 g), and the mixture is subjected to catalytic hydrogenation at room temperature under atmospheric pressure. The mixture is filtered, and the filtrate is concentrated under reduced pressure to remove the solvent to give 2-(1-pyrrolidinyl)carbonylpyrrolidine (about 18 g) as an oily product.

Lithium aluminum hydride (9 g) is suspended in dry tetrahydrofuran (100

ml) under ice-cooling, and thereto is added dropwise a solution of 2-(1-pyrrolidinyl)carbonylpyrrolidine (33 g) in dry tetrahydrofuran (80 ml). The mixture is refluxed under nitrogen atmosphere for four hours. The mixture is cooled with ice, and thereto is added a saturated aqueous sodium sulfate solution (about 15 ml), and then mixture is further stirred at room temperature for three hours. The precipitated sodium sulfate is removed by filtration, washed well with chloroform. The filtrate and the washings are combined, concentrated under reduced pressure, and evaporated to give 2-(1-pyrrolidinyl)methyl-pyrrolidine (22 g).

Colorless oil

B.p. 99-101°C (20 mmHg)

Reference Example 9

4-Benzyl-2-chloromethylmorpholine (15 g) and 4-(2-hydroxyethyl)-piperazine (25 ml) are mixed, and the mixture is heated with stirring at 130°C for five hours. After the reaction is complete, the mixture is extracted with chloroform, and the extract is dried over magnesium sulfate. The residue thus obtained is concentrated under reduced pressure to give 4-benzyl-2-[4-(2-hydroxyethyl)-1-piperazinyl]methylmorpholine (16 g).

^{1}H-NMR ($CDCl_3$) δppm: 1.86 (1H, t, J=10.6Hz), 2.07-2.27 (2H, m), 2.37-3.05 (14H, m), 3.49 (2H, d, J=2.3Hz), 3.57-3.89 (5H, m), 7.24-7.33 (5H, m)

4-Benzyl-2- ydroxyethyl)-1-piperazinyl]methylmorpholine (16 g) is dissolved in ethar ml), and thereto is added palladium hydroxide (1.6 g). The mixture is subjected to de-benzylation at 50°C under hydrogen atmosphere. Five hours later, the mixture is filtered through a cerite pad, and the

filtrate is concentrated under reduced pressure. The resulting crystals are washed with diethyl ether-n-hexane to give 2-[4-(2-hydroxyethyl)-1-piperazinyl]methylmorpholine (9.09 g).

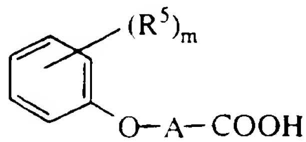
M.p. 73-75.5°C

White powder

^{1}H-NMR ($CDCl_3$) δppm: 2.25 (1H, dd, J=4.2Hz, J=13.0Hz), 2.37-2.74 (11H, m), 2.74-3.02 (6H, m), 3.49-3.77 (4H, m), 3.85-3.93 (1H, m)

Using the suitable starting compounds, the compounds as listed in Tables 1 to 4 are obtained in the same manner as in Reference Example 1.

Table 1



Reference Example 10

R^5: CH_3 (2-position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (1)

Reference Example 11

R^5: C_2H_5 (2-position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (2)

Reference Example 12

R^5: $-(CH_2)_2CH_3$ (2-position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (3)

Reference Example 13

R^5: $-(CH_2)_3CH_3$ (2-position)	m: 1	A: $-CH_2-$
M.p. 102-104°C	Solvent for recrystallization: Ethanol-water	
Crystalline form: White powder	Form: Free	

Table 2

Reference Example 14		
R^5: $-(CH_2)_4CH_3$ (2-position)	m: 1	A: $-CH_2-$
M.p. 71.4-74.4°C	Solvent for recrystallization: Ethanol-water	
Crystalline form: White powder	Form: Free	
Reference Example 15		
R^5: F (2-position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (4)
Reference Example 16		
R^5: Cl (2-position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (5)
Reference Example 17		
R^5: $-(CH_2)_4-$ (combined at 2- and 3-positions)		
m: 2	A: $-CH_2-$	
Crystalline form: White powder	Form: Free	NMR (6)
Reference Example 18		
R^5: CH_3 (2- and 3-positions)	m: 2	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (7)

Table 3

Reference Example 19		
R^5: CH_3 (2- and 6–positions)	m: 2	A: $-CH_2-$
Crystalline form: Yellow powder	Form: Free	NMR (8)
Reference Example 20		
R^5: CH_3 (3- and 5–positions)	m: 2	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (9)
Reference Example 21		
R^5: CH_3 (3–position)	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (10)
Reference Example 22		
R^5: C_2H_5 (3–position)	m: 1	A: $-CH_2-$
M.p. 102-104°C	Solvent for recrystallization: Ethanol-water	
Crystalline form: White powder	Form: Free	
Reference Example 23		
R^5: $-(CH_2)_2CH_3$ (3–position)	m: 1	A: $-CH_2-$
M.p. 63.5-66.0°C	Solvent for recrystallization: Ethanol-water	
Crystalline form: White powder	Form: Free	

Table 4

Reference Example 24

R^5: $-(CH_2)_3CH_3$ (3–position) m: 1 A: $-CH_2-$

M.p. 69.0-72.5°C Solvent for recrystallization: Ethanol-water

Crystalline form: Colorless prisms Form: Free NMR (11)

Reference Example 25

R^5: $-CH(CH_3)_2$ (3–position) m: 1 A: $-CH_2-$

Crystalline form: White solid Form: Free NMR (12)

Reference Example 26

R^5: Cl (3–position) m: 1 A: $-CH_2-$

Crystalline form: White powder Form: Free NMR (13)

Reference Example 27

R^5: F (3–position) m: 1 A: $-CH_2-$

Crystalline form: White powder Form: Free NMR (14)

Reference Example 28

R^5: CH_3O (3–position) m: 1 A: $-CH_2-$

Crystalline form: Beige powder Form: Free NMR (15)

Reference Example 29

R^5: C_2H_5O (3–position) m: 1 A: $-CH_2-$

Crystalline form: Beige powder Form: Free NMR (16)

^{1}H-NMR spectrum (NMR (1) to NMR (17)) as described in Tables 1 to 4 are as follows:

NMR (1) (DMSO-d_6) δppm: 2.19 (3H, s), 4.68 (2H, s), 6.83 (2H, dd, J=7.8Hz, J=13.2Hz), 7.12 (2H, t, J=7.8Hz), 12.96 (1H, s)

NMR (2) (DMSO-d_6) δppm: 1.14 (3H, t,, J=7.5Hz), 2.61 (2H, q, J=7.5Hz), 4.69 (2H, s), 6.78-6.95 (2H, m), 7.05-7.20 (2H, m), 12.97 (1H, s)

NMR (3) ($CDCl_3$) δppm: 0.95 (3H, t, J=7.4Hz), 1.5-1.8 (2H, m), 2.65 (2H, t, J=7.4Hz), 4.65 (2H, s), 6.73 (1H, d, J=8.3Hz), 6.9-7.05 (1H, m), 7.15 (2H, t, J=7.2Hz), 9.4-10.1 (1H, m)

NMR (4) (DMSO-d_6) δppm: 4.77 (2H, s), 6.88-7.30 (4H, m), 13.09 (1H, s)

NMR (5) ($CDCl_3$) δppm: 4.76 (2H, s), 6.89 (1H, dd, J=1.5Hz, J=8.0Hz), 6.99 (1H, dt, J=1.5Hz, J=7.6Hz), 7.23 (1H, dt, J=1.5Hz, J=7.6Hz), 7.41 (1H, dd, J=1.5Hz, J=8.0Hz), 8.16 (1H, br)

NMR (6) (DMSO-d_6) δppm: 1.6-1.85 (4H, m), 2.55-2.75 (4H, m), 4.63 (2H, s), 6.57 (1H, d, J=8Hz), 6.65 (1H, d, J=7.5Hz), 6.9-7.05 (1H, m), 12.94 (1H, br)

NMR (7) (DMSO-d_6) δppm: 2.10 (3H, s), 2.20 (3H, s), 4.63 (2H, s), 6.64 (1H, d, J=8Hz), 6.75 (1H, d, J=7.5Hz), 6.95-7.1 (1H, m), 12.9 (1H, br)

NMR (8) (DMSO-d_6) δppm: 2.22 (6H, s), 4.35 (2H, s), 6.87-7.06 (3H, m), 12.87 (1H, s)

NMR (9) (DMSO-d_6) δppm: 2.22 (6H, s), 4.48 (2H, s), 6.48 (2H, s), 6.60 (1H, s)

NMR (10) (DMSO-d_6) δppm: 2.26 (3H, s), 4.62 (2H, s), 6.60-6.80 (3H, m), 7.11-7.18 (1H, m)

NMR (11) (DMSO-d_6) δppm: 0.85 (3H, t, J=7.2Hz), 1.17-1.38 (2H, m), 1.45-1.60 (2H, m), 2.49-2.57 (2H, m), 4.63 (2H, s), 6.66-6.79 (3H, m), 7.13-7.21 (1H, m), 13.00 (1H, br)

NMR (12) ($CDCl_3$) δppm: 1.22 (6H, d, J=6.9Hz), 2.77-3.00 (1H, m), 4.68 (2H, s), 6.66-6.76 (1H, m), 6.81-6.95 (2H, m), 7.17-7.29 (1H, m), 8.65 (1H, brs)

NMR (13) ($CDCl_3$) δppm: 4.69 (2H, s), 6.79-6.85 (1H, m), 6.85-7.04 (2H, m), 7.19-7.28 (1H, m), 8.00 (1H, br)

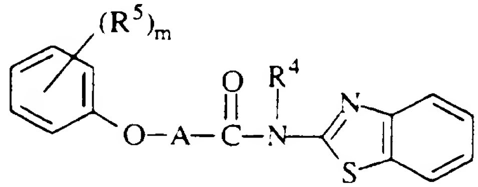
NMR (14) ($CDCl_3$) δppm: 4.69 (2H, s), 6.62-6.79 (3H, m), 7.20-7.32 (1H, m), 9.07 (1H, br)

NMR (15) ($CDCl_3$) δppm: 3.79 (3H, s), 4.67 (2H, s), 6.47-6.61 (3H, m), 7.16-7.26 (1H, m), 9.12 (1H, br)

NMR (16) ($CDCl_3$) δppm: 1.40 (3H, t, J=7.0Hz), 4.01 (2H, q, J=7.0Hz), 4.66 (2H, s), 6.45-6.62 (3H, m), 7.13-7.25 (1H, m), 8.34 (1H, br)

Using the suitable starting compounds, the compounds as listed in Tables 5-9 are obtained in the same manner as Reference Example 2.

Table 5



Reference Example 30

R^5: CH_3 (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (1)

Reference Example 31

R^5: C_2H_5 (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow powder Form: Free NMR (2)

Reference Example 32

R^5: $-(CH_2)_2CH_3$ (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (3)

Reference Example 33

R^5: $-(CH_2)_3CH_3$ (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow solid Form: Free NMR (4)

Table 6

Reference Example 34

R^5: H (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow powder Form: Free NMR (5)

Reference Example 35

R^5: $-(CH_2)_4CH_3$ (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (6)

Solvent for recrystallization: Ethyl acetate-n-hexane

Reference Example 36

R^5: F (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow powder Form: Free NMR (7)

Reference Example 37

R^5: Cl (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (8)

Reference Example 38

R^5: $-(CH_2)_4-$ (combined at 2– and 3-positions)

m: 2 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (9)

Table 7

Reference Example 39

R^5: CH_3 (2– and 3-positions)

m: 2 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (10)

Reference Example 40

R^5: CH_3 (2– and 6-positions)

m: 2 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (11)

Reference Example 41

R^5: CH_3 (3– and 5-positions)

m: 2 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (12)

Reference Example 42

R^5: $-(CH_2)_3Cl$ (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow powder Form: Free NMR (13)

Reference Example 43

R^5: $-(CH_2)_2Cl$ (2–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (14)

Table 8

Reference Example 44

R^5: CH_3 (3–position) m: 1 A: $-CH_2-$ R^4: H

Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: Pale brown powder Form: Free NMR (15)

Reference Example 45

R^5: C_2H_5 (3–position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Beige needles Form: Free NMR (16)

Reference Example 46

R^5: $-(CH_2)_2CH_3$ (3–position) m: 1 A: $-CH_2-$ R^4: H

M.p. 110.0-111.0°C Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: Pale yellow needles Form: Free

Reference Example 47

R^5: $-(CH_2)_3CH_3$ (3–position) m: 1 A: $-CH_2-$ R^4: H

M.p. 110.5-111.0°C Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: Pale yellow needles Form: Free

Reference Example 48

R^5: $-CH\genfrac{}{}{0pt}{}{\diagup CH_3}{\diagdown CH_3}$ (3–position) m: 1 A: $-CH_2-$ R^4: H

M.p. 93.7-94.0°C Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: Pink powder Form: Free

Table 9

Reference Example 49			
R^5: Cl (3–position)	m: 1	A: $-CH_2-$	R^4: H
Crystalline form: Pale yellow powder		Form: Free	NMR (17)
Reference Example 50			
R^5: F (3–position)	m: 1	A: $-CH_2-$	R^4: H
Crystalline form: Pale yellow powder		Form: Free	NMR (18)
Reference Example 51			
R^5: CH_3O (3–position)	m: 1	A: $-CH_2-$	R^4: H
Crystalline form: Beige powder		Form: Free	NMR (19)
Reference Example 52			
R^5: C_2H_5O (3–position)	m: 1	A: $-CH_2-$	R^4: H
Crystalline form: Brown powder		Form: Free	NMR (20)

^{1}H-NMR spectrum (NMR (1) to NMR (20)) as described in Tables 5 to 9 are as follows:

NMR (1) (DMSO-d_6) δppm: 2.45 (3H, s), 4. 95 (2H, s), 6.81-6.95 (2H, m), 7.10-7.22 (2H, m), 7.32 (1H, t, J=6.1Hz), 7.45 (1H, t, J=6.4Hz), 7.77 (1H, d, J=6.4Hz), 7.99 (1H, d, J=6.3Hz), 12.60 (1H, s)

NMR (2) (DMSO-d_6) δppm: 1.18 (3H, t, J=7.5Hz), 2.67 (2H, q, J=7.5Hz), 4.96 (2H, s), 6.89 (2H, dd, J=8.0Hz, J=12.5Hz), 7.09-7.23 (2H, m), 7.28-7.38 (1H, m), 7.40-7.52 (1H, m), 7.77 (1H, d, J=8.0Hz), 7.98 (1H, d, J=7.8Hz), 12.58 (1H, s)

NMR (3) ($CDCl_3$) δppm: 1.03 (3H, t, J=7.4Hz), 1.6-1.8 (2H, m), 2.73 (2H, t, J=7.4Hz), 4.76 (2H, s), 6.84 (1H, d, J=8.0Hz), 7.01-7.50 (5H, m), 7.79-7.86 (2H, m), 9.6-9.8 (1H, s)

NMR (4) ($CDCl_3$) δppm: 0.95 (3H, t J=7.2Hz), 1.37-1.55 (2H, m), 1.59-1.74 (2H, m), 2.71 (2H, d, J=7.2Hz), 4.77 (2H, s), 6.82 (1H, d, J=8.1Hz), 6.98-7.06 (1H, m), 7.16-7.26 (2H, m), 7.30-7.38 (1H, m), 7.41-7.50 (1H, m), 7.79-7.86 (2H, m), 9.78 (1H, brs)

NMR (5) ($CDCl_3$) δppm: 4.76 (2H, s), 6.95-7.11 (3H, m), 7.26-7.47 (4H, m), 7.79-7.87 (2H, m), 9.92 (1H, br)

NMR (6) ($CDCl_3$) δppm: 0.92 (3H, t, J=6.8Hz), 1.30-1.55 (4H, m), 1.55-1.90 (2H, m), 2.71 (2H, t, J=7.6Hz), 4.77 (2H, s), 6.82 (1H, d, J=8.0Hz), 6.98-7.05 (1H, m), 7.17-7.26 (2H, m), 7.31-7.38 (1H, m), 7.42-7.50 (1H, m), 7.79-7.87 (2H, m), 9.73 (1H, brs)

NMR (7) (DMSO-d_6) δppm: 5.03 (2H, s), 6.90-7.07 (1H, m), 7.07-7.20 (2H, m), 7.20-7.50 (2H, m), 7.45 (1H, dt, J=1.3Hz, J=7.3Hz), 7.77 (1H, d, J=7.8Hz), 7.99 (1H, dd, J=0.7Hz, J=7.7Hz), 12.63 (1H, s)

NMR (8) ($CDCl_3$) δppm: 4.80 (2H, s), 6.95-7.10 (2H, m), 7.23-7.49 (4H, m), 7.85 (2H, dd, J=2.0Hz, J=6.6Hz), 9.97 (1H, br)

NMR (9) ($CDCl_3$) δppm: 1.75-2.0 (4H, m), 2.75-2.9 (4H, m), 4.74 (2H, s), 6.63 (1H, d, J=8Hz), 6.82 (1H, d, J=8Hz), 7.05-7.15 (1H, m), 7.3-7.5 (2H, m), 7.75-7.9 (2H, m), 9.73 (1H, br)

NMR (10) ($CDCl_3$) δppm: 2.29 (3H, s), 2.32 (3H, s), 4.75 (2H, s), 6.70 (1H, d, J=8Hz), 6.90 (1H, d, J=7.5Hz), 7.05-7.15 (1H, m), 7.3-7.5 (2H, m), 7.75-7.9 (2H,

m), 9.76 (1H, br)

NMR (11) (DMSO-d_6) δppm: 2.27 (6H, s), 4.63 (2H, s), 6.90-7.12 (3H, s), 7.29-7.40 (1H, m), 7.42-7.52 (1H, s), 7.76 (1H, d, J=7.8Hz), 8.02 (1H, d, J=7.4 Hz), 12.49 (1H, s)

NMR (12) ($CDCl_3$) δppm: 2.32 (6H, s), 4.73 (2H, s), 6.61 (2H, s), 6.72 (1H, s), 7.3-7.55 (2H, m), 7.8-7.95 (2H, m), 9.86 (1H, br)

NMR (13) ($CDCl_3$) δppm: 2.18 (2H, tt, J=7.0Hz, J=8.0Hz), 2.96 (2H, t, J=7.0Hz), 3.63 (2H, t, J=8.0Hz), 4.80 (2H, s), 6.87 (1H, d, J=8.5Hz), 7.04 (1H, t, J=7.2Hz), 7.15-7.29 (2H, m), 7.34 (1H, t, J=8.9Hz), 7.43 (1H, t, J=8.0Hz), 7.79-7.87 (2H, m), 9.73 (1H, br)

NMR (14) ($CDCl_3$) δppm: 3.22 (2H, t, J=7.0Hz), 3.82 (2H, t, J=7.0Hz), 4.81 (2H, s), 6.86 (1H, d, J=8.2Hz), 7.05 (1H, t, J=7.2Hz), 7.15-7.52 (4H, m), 7.81 (2H, t, J=8.4Hz), 9.78 (1H, br)

NMR (15) ($CDCl_3$) δppm: 2.37 (3H, s), 4.74 (2H, s), 6.74-6.85 (2H, m), 6.85 (1H, d, J=7.3Hz), 7.17-7.30 (1H, m), 7.30-7.40 (1H, m), 7.40-7.54 (1H, m), 7.77-7.90 (2H, m), 9.88 (1H, brs)

NMR (16) ($CDCl_3$) δppm: 1.25 (3H, t, J=7.6Hz), 2.65 (2H, q, J=7.6Hz), 4.74 (2H, s), 6.74-6.84 (2H, m), 6.88-6.95 (1H, m), 7.21-7.50 (3H, m), 7.79-7.86 (2H, m), 9.94 (1H, br)

NMR (17) ($CDCl_3$) δppm: 4.73 (2H, s), 6.75-6.84 (1H, m), 6.84-6 (1H, m), 7.01-7.08 (1H, m), 7.21-7 6 (3H, m), 7.82 (2H, t, J=8.4Hz), 10.09 (1H, br)

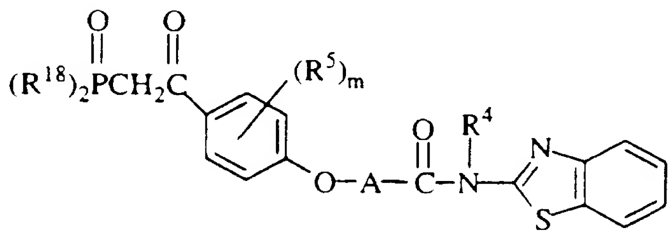
NMR (18) (DMSO-d_6) δppm: 4.94 (2H, s), 6.75-6.92 (3H, m), 7.27-7.47 (3H, m), 7.75 (1H, d, J=8.0Hz), 7.97 (1H, d, J=8.0Hz)

NMR (19) ($CDCl_3$) δppm: 3.81 (3H, s), 4.73 (2H, s), 6.53-6.65 (3H, m), 7.20-7.51 (3H, m), 7.79-7.86 (2H, m), 9.89 (1H, br)

NMR (20) ($CDCl_3$) δppm: 1.43 (3H, t, J=7.0Hz), 4.04 (2H, q, J=7.0Hz), 4.73 (2H, s), 6.50-6.66 (3H, m), 7.18-7.51 (3H, m), 7.78-7.90 (2H, m), 9.87 (1H, br)

Using the suitable starting compounds, the compounds as listed in Table 10 are obtained in the same manner as in Reference Example 3.

Table 10



Reference Example 53

R^5: C_2H_5O (2–position) m: 1 A: $-CH_2-$ R^4: H R^{18}: CH_3O

Crystalline form: Pale yellow powder Form: Free NMR (1)

Reference Example 54

R^5: $-OCH(CH_3)_2$ (3–position) m: 1 A: $-CH_2-$

R^4: H R^{18}: CH_3O

Crystalline form: White powder Form: Free NMR (2)

Reference Example 55

R^5: CF_3CH_2O (3–position) m: 1 A: $-CH_2-$

R^4: H R^{18}: CH_3O

Crystalline form: White powder Form: Free NMR (3)

Reference Example 56

R^5: CF_3 (2–position) m: 1 A: $-CH_2-$ R^4: H R^{18}: CH_3O

Crystalline form: White powder Form: Free NMR (4)

Reference Example 57

R^5: CH_3O (3–position) m: 1 A: $-CH_2-$ R^4: H R^{18}: CH_3O

Crystalline form: White powder Form: Free NMR (5)

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^{1}H-NMR spectrum (NMR (1) to NMR (5)) as described in Table 10 are as follows:

NMR (1) ($CDCl_3$) δppm: 1.58 (3H, t, J=7.0Hz), 3.61 (2H, d, J=22.8Hz), 3.76 (3H, s), 3.82 (3H, s), 4.25 (2H, q, J=7.0Hz), 4.85 (2H, s), 7.04 (1H, d, J=8.6Hz), 7.33 (1H, t, J=7.5Hz), 7.46 (1H, t, J=7.5Hz), 7.60-7.65 (2H, m), 7.79-7.86 (2H, m), 10.28 (1H, br)

NMR (2) ($CDCl_3$) δppm: 1.47 (6H, d, J=6.0Hz), 3.74 (3H, s), 3.79 (3H, s), 3.85 (2H, d, J=20.2Hz), 4.69 (1H, sept, J=6.0Hz), 4.79 (2H, s), 6.51-6.56 (2H, m), 7.36 (1H, t, J=7.0Hz), 7.49 (1H, t, J=7.0Hz), 7.79-7.88 (3H, m), 9.98 (1H, br)

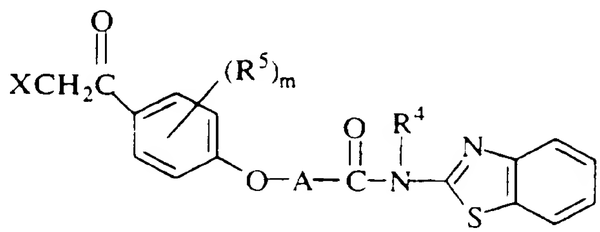
NMR (3) ($CDCl_3$) δppm: 3.76 (2H, d, J=21.3Hz), 3.75 (3H, s), 3.80 (3H, s), 4.40 (2H, q, J=7.9Hz), 4.79 (2H, s), 6.44 (1H, d, J=2.2Hz), 6.60 (1H, dd, J=2.2Hz, J=8.8Hz), 7.34 (1H, dt, J=1.3Hz, J=7.3Hz), 7.45 (1H, dt, J=1.3Hz, J=7.3Hz), 7.75-7.86 (3H, m)

NMR (4) (DMSO-d_6) δppm: 3.62 (3H, s), 3.68 (3H, s), 3.93 (2H, d, J=22.5Hz), 5.27 (2H, s), 7.3-7.55 (3H, m), 7.78 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 8.2-8.35 (2H, m), 12.68 (1H, br)

NMR (5) ($CDCl_3$) δppm: 3.74 (3H, s), 3.80 (3H, s), 3.81 (2H, d, J=21Hz), 3.95 (3H, s), 4.81 (2H, s), 6.5-6.65 (2H, m), 7.25-7.55 (2H, m), 7.75-7.95 (3H, m), 10.01 (1H, s)

Using the suitable starting compounds, the compounds as listed in Tables 11-13 are obtained in the same manner as in Reference Example 4.

Table 11



Reference Example 58

R^5: H m: 1 A: $-CH_2-$ R^4: H X: Br

Crystalline form: Pale yellow powder Form: Free NMR (1)

Reference Example 59

R^5: CH_3 (2-position) m: 1 A: $-CH_2-$ R^4: H X: Cl

Crystalline form: Beige powder Form: Free NMR (2)

Reference Example 60

R^5: C_2H_5 (2-position) m: 1 A: $-CH_2-$ R^4: H X: Cl

Crystalline form: Beige powder Form: Free NMR (3)

Reference Example 61

R^5: $-(CH_2)_3CH_3$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Cl

Crystalline form: White powder Form: Free NMR (4)

Table 12

Reference Example 62

R^5: Cl (2-position) m: 1 A: $-CH_2-$ R^4: H X: Cl

M.p. 199-201°C

Solvent for recrystallization: 1,2-Dichloroethane-n-hexane

Crystalline form: White powder Form: Free

Reference Example 63

R^5: $-(CH_2)_2Cl$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Br

Crystalline form: Pale yellow powder Form: Free NMR (5)

Reference Example 64

R^5: $-(CH_2)_3Cl$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Br

Crystalline form: Pale yellow powder Form: Free NMR (6)

Reference Example 65

R^5: $-(CH_2)_4Cl$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Cl

M.p. 146.5-149°C Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: White powder Form: Free

Table 13

Reference Example 66

R^5: $-(CH_2)_2CO_2C_2H_5$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Cl

M.p. 131.0-133.0°C

Solvent for recrystallization: Ethyl acetate-n-hexane

Crystalline form: White powder Form: Free

Reference Example 67

R^5: $-(CH_2)_2CO_2CH_3$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Cl

Crystalline form: White powder Form: Free NMR (7)

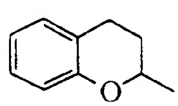
Reference Example 68

R^5: $-CH_2CH(OCOCH_3)CH_2OCOCH_3$ (2-position) m: 1 A: $-CH_2-$

R^4: H X: Cl

Crystalline form: White powder Form: Free NMR (8)

Reference Example 69

R^5 and A combine to form: 

m: 1 R^4: H X: Cl

M.p. 206-208°C

Solvent for recrystallization: Dimethylformamide-ethanol

Crystalline form: White powder Form: Free

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^{1}H-NMR spectrum (NMR (1) to NMR (8)) as described in Tables 11-13 are as follows:

NMR (1) ($CDCl_3$) δppm: 4.41 (2H, s), 4.84 (2H, s), 7.07 (2H, d, J=9.0Hz), 7.36 (1H, t, J=7.3Hz), 7.45 (1H, t, J=7.3Hz), 7.88 (2H, t, J=8.5Hz), 8.03 (2H, d, J=9.0Hz)

NMR (2) (DMSO-d_6) δppm: 2.30 (3H, s), 5.11 (4H, s), 7.00-7.10 (1H, m), 7.28-7.40 (1H, m), 7.40-7.55 (1H, m), 7.70-7.93 (3H, m), 7.98 (1H, d, J=7.1Hz), 12.68 (1H, s)

NMR (3) (DMSO-d_6) δppm: 1.21 (3H, t, J=7.4Hz), 2.72 (2H, q, J=7.4Hz), 5.12, 5.13 (4H, each s), 7.02 (1H, d, J=8.6Hz), 7.31 (1H, dt, J=1.2Hz, J=7.3Hz), 7.45 (1H, dt, J=1.3Hz, J=7.3Hz), 7.75-7.92 (3H, m), 7.95-8.00 (1H, m), 12.68 (1H, brs)

NMR (4) ($CDCl_3$) δppm: 0.97 (3H, t, J=7.2Hz), 1.39-1.59 (2H, m), 1.59-1.86 (2H, m), 2.77 (2H, t, J=7.6Hz), 4.67 (2H, s), 4.86 (2H, s), 6.89 (1H, d, J=8.6Hz), 7.32-7.39 (1H, m), 7.43-7.51 (1H, m), 7.79-7.87 (4H, m), 9.10-10.01 (1H, brs)

NMR (5) ($CDCl_3$) δppm: 3.16 (2H, t, J=6.9Hz), 3.92 (2H, t, J=6.9Hz), 4.83 (2H, s), 5.13 (2H, s), 7.07 (1H, d, J=9.4Hz), 7.31 (1H, t, J=6.9Hz), 7.45 (1H, t, J=8.3Hz), 7.76 (1H, d, J=7.9Hz), 7.82-8.06 (3H, m)

NMR (6) ($CDCl_3$) δppm: 2.17 (2H, tt, J=6.1Hz, J=7.5Hz), 3.03 (2H, t, J=7.5Hz), 3.64 (2H, t, J=6.1Hz), 4.40 (2H, s), 4.88 (2H, s), 6.95 (1H, d, J=9.3Hz), 7.35 (1H, t, J=6.8Hz), 7.47 (1H, t, J=9.4Hz), 7.80-7.94 (4H, m), 9.68 (1H, br)

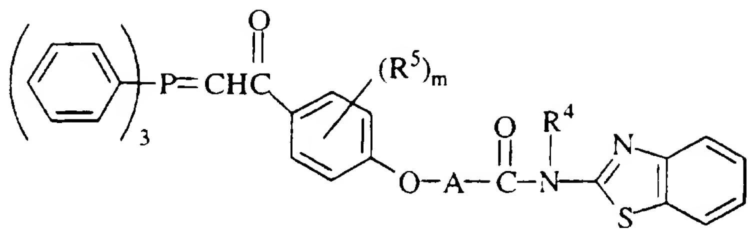
NMR (7) ($CDCl_3$) δppm: 2.75 (2H, t, J=7.0Hz), 3.13 (2H, t, J=7.0Hz), 3.74

(3H, s), 4.65 (2H, s), 4.89 (2H, s), 6.89 (1H, d, J=8.4Hz), 7.30-7.37 (1H, m), 7.41-7.48 (1H, m), 7.78-7.89 (4H, m), 9.00-11.30 (1H, brs)

NMR (8) ($CDCl_3$) δppm: 2.00 (3H, s), 2.09 (3H, s), 3.08 (1H, dd, J=8Hz, J=14Hz), 3.23 (1H, dd, J=6Hz, J=14Hz), 4.14 (1H, dd, J=5.5Hz, J=12Hz), 4.33 (1H, dd, J=3Hz, J=12Hz), 4.64 (2H, s), 4.5 (2H, s), 5.49 (1H, m), 6.90 (1H, d, J=9Hz), 7.3-8.0 (6H, m), 8.79 (1H, br)

Using the suitable starting compounds, the compounds as listed in Tables 14-22 are obtained in the same manner as in Reference Example 5 or 6.

Table 14



Reference Example 70

R^5: H m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow amorphous Form: Free NMR (1)

Reference Example 71

R^5: CH_3 (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow amorphous Form: Free NMR (2)

Reference Example 72

R^5: C_2H_5 (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (3)

Reference Example 73

R^5: $-CH(CH_3)CH_3$ (3-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (4)

Table 15

Reference Example 74

R^5: $-(CH_2)_3CH_3$ (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow powder Form: Free NMR (5)

Reference Example 75

R^5: Cl (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow amorphous Form: Free NMR (6)

Reference Example 76

R^5: F (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (7)

Reference Example 77

R^5: $-(CH_2)_2Cl$ (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (8)

Reference Example 78

R^5: $-(CH_2)_4Cl$ (2-position) m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White needles Form: Free NMR (9)

Table 16

Reference Example 79

R^5: $-(CH_2)_2CO_2C_2H_5$ (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (10)

Reference Example 80

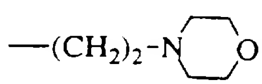
R^5: $-CH_2CH(OCOCH_3)CH_2OCOCH_3$ (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (11)

Reference Example 81

R^5:



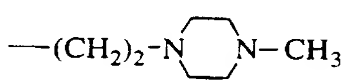
(2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (12)

Reference Example 82

R^5:



(2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow amorphous Form: Free NMR (13)

Table 17

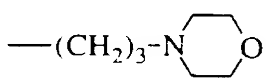
Reference Example 83

R^5: $-(CH_2)_3N(C_2H_5)_2$ (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (14)

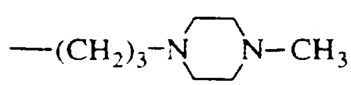
Reference Example 84

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (15)

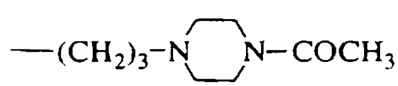
Reference Example 85

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (16)

Reference Example 86

R^5:  (2-position) m: 1

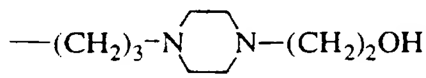
A: $-CH_2-$ R^4: H

M.p. 153-155°C Solvent for recrystallization: Ethyl acetate

Crystalline form: White powder Form: Free

Table 18

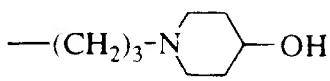
Reference Example 87

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (17)

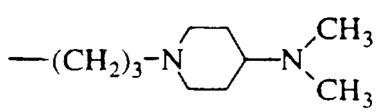
Reference Example 88

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (18)

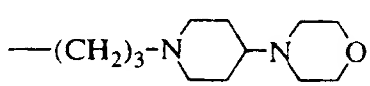
Reference Example 89

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: Colorless amorphous Form: Free NMR (19)

Reference Example 90

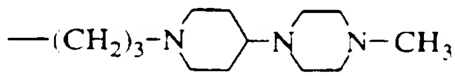
R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: Colorless amorphous Form: Free NMR (20)

Table 19

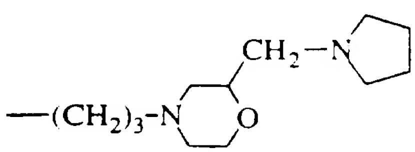
Reference Example 91

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow amorphous Form: Free NMR (21)

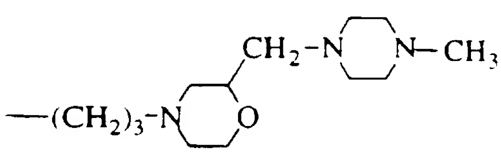
Reference Example 92

R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: Colorless amorphous Form: Free NMR (22)

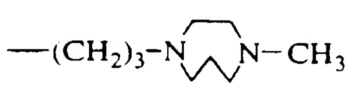
Reference Example 93

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow amorphous Form: Free NMR (23)

Reference Example 94

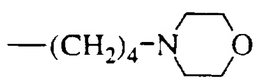
R^5:  (2-position) m: 1

A: $-CH_2-$ R^4: H

Crystalline form: Yellow amorphous Form: Free NMR (24)

Table 20

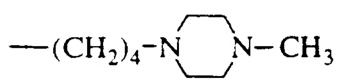
Reference Example 95

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White powder Form: Free NMR (25)

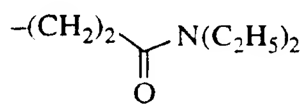
Reference Example 96

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow powder Form: Free NMR (26)

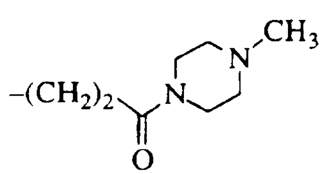
Reference Example 97

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (27)

Reference Example 98

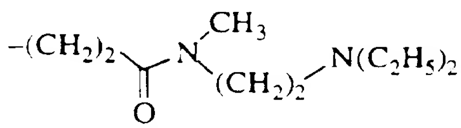
R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (28)

Table 21

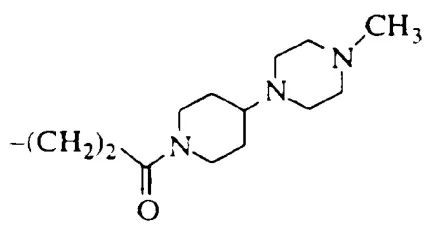
Reference Example 99

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (29)

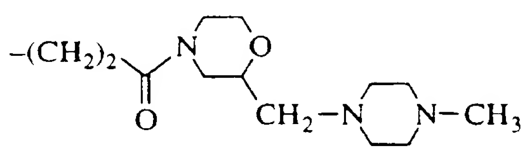
Reference Example 100

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: White amorphous Form: Free NMR (30)

Reference Example 101

R^5:  (2-position)

m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Yellow amorphous Form: Free NMR (31)

Reference Example 102

R^5: $-COOCH_3$ (2-position m: 1 A: $-CH_2-$ R^4: H

Crystalline form: Pale yellow amorphous Form: Free NMR (32)

Table 22

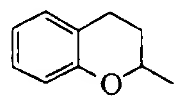
Reference Example 103

R^5: $-(CH_2)_2CONH-$ (combined at 2- and 3-positions)

m: 2 A: $-CH_2-$ R^4: H

Crystalline form: Yellow amorphous Form: Free NMR (33)

Reference Example 104

R^5 and A combine to form: 

m: 1 R^4: H

Crystalline form: White powder Form: Free NMR (35)

---

^1H-NMR spectrum (NMR (1) to NMR (35)) as described in Tables 14-22 are as follows:

NMR (1) ($CDCl_3$) δppm: 4.37 (1H, d, J=24Hz), 4.77 (2H, s), 6.91 (2H, d, J=8.8Hz), 7.16 (1H, t, J=7.3Hz), 7.32 (1H, t, J=7.3Hz), 7.38-7.82 (17H, m), 7.89 (2H, d, J=8.8Hz)

NMR (2) ($CDCl_3$) δppm: 2.35 (3H, s), 4.41 (1H, brs), 4.70 (2H, s), 6.70 (1H, d, J=8.2Hz), 7.20-8.00 (21H, m)

NMR (3) (DMSO-d_6) δppm: 1.19 (3H, t, J=7.4Hz), 2.69 (2H, q, J=7.4Hz), 4.43 (1H, d, J=2.5Hz), 5.00 (2H, s), 6.83 (1H, d, J=8.9Hz), 7.25-7.38 (1H, m), 7.38-7.85 (19H, m), 7.98 (1H, d, J=7.1Hz), 12.65 (1H, brs)

NMR (4) ($CDCl_3$) δppm: 1.32 (6H, d, J=7Hz), 3.42 (1H, sept, J=7Hz), 4.2-4.6 (1H, m), 4.73 (2H, s), 7.25-8.0 (21H, m), 10.01 (1H, br)

NMR (5) ($CDCl_3$) δppm: 0.86 (3H, t, J=7.2Hz), 1.31-1.51 (2H, m), 1.51-1.72 (2H, m), 2.65-2.72 (2H, m), 3.76 (3H, s), 4.34 (1H, br-d, J=24.7Hz), 4.66 (2H, s), 5.98 (1H, br-s), 6.66 (1H, d, J=8.3Hz), 6.99-7.10 (1H, m), 7.19-7.31 (1H, m), 7.38-7.60 (11H, m), 7.60-7.87 (8H, m)

NMR (6) (DMSO-d_6) δppm: 4.52 (1H, d, J=23Hz), 5.12 (2H, s), 7.07 (1H, d, J=8.4Hz), 7.31 (1H, td, J=7.6Hz, J=1.0Hz), 7.45 (1H, td, J=7.6Hz, J=1.4Hz), 7.45-8.15 (19H, m), 12.68 (1H, s)

NMR (7) ($CDCl_3$) δppm: 4.34 (1H, d, J=22Hz), 4.79 (2H, s), 6.97 (1H, t, J=8.4Hz), 7.30-7.38 (2H, m), 7.38-7.92 (19H, m), 9.97 (1H, br)

NMR (8) (DMSO-d_6) δppm: 3.16 (2H, t, J=7.0Hz), 3.92 (2H, t, J=7.0Hz), 4.83 (2H, s), 5.13 (2H, s), 7.07 (1H, d, J=9.4Hz), 7.34 (1H, t, J=6.5Hz), 7.44 (1H, t, J=6.5Hz), 7.60-8.12 (19H, m), 12.70 (1H, br)

NMR (9) ($CDCl_3$) δppm: 1.67-1.90 (4H, m), 2.64-2.82 (2H, m), 3.68 (1H, bt, J=6.0Hz), 5.19 (2H, s), 6.12 (2H, d, J=14.0Hz), 7.10 (1H, d, J=10.0Hz), 7.29-7.41 (1H, m), 7.41-7.52 (1H, m), 7.69-7.95 (17H, m), 7.95-8.06 (2H, m), 12.74 (1H, br-s)

NMR (10) (DMSO-d_6) δppm: 1.10 (3H, t, J=7.1Hz), 2.62 (2H, t, J=8.0Hz), 2.90 (2H, t, J=8.0Hz), 4.00 (2H, q, J=7.1Hz), 4.33 (1H, d, J=30.0Hz), 5.01 (2H, s), 6.82 (1H, d, J=14.0Hz), 7.29-7.38 (1H, m), 7.40-7.50 (1H, m), 7.50-7.80 (18H, m), 8.00-8.02 (1H, d, J=4.0Hz), 12.61 (1H, brs)

NMR (11) ($CDCl_3$) δppm: 2.00 (3H, s), 2.05 (3H, s), 3.0-3.15 (2H, m), 4.0-4.35 (2H, m), 4.93, 5.05 (2H, ABq, J=16Hz), 5.40 (1H, m), 6.1-6.6 (2H, br), 6.98 (1H, d, J=8Hz), 7.2-8.5 (2H, m)

NMR (12) ($CDCl_3$) δppm: 2.54-2.78 (6H, m), 2.87-3.12 (2H, m), 3.69-3.90

(4H, m), 4.36 (1H, d, J=24.0Hz), 4.78 (2H, s), 6.77 (1H, d, J=8.5Hz), 7.27-7.88 (21H, m)

NMR (13) ($CDCl_3$) δppm: 2.27 (3H, s), 2.32-2.76 (10H, m), 2.76-3.05 (2H, m), 4.36 (1H, d, J=26.0Hz), 4.71 (2H, s), 6.77 (1H, d, J=8.3Hz), 7.27-8.02 (21H, m)

NMR (14) ($CDCl_3$) δppm: 1.00 (6H, t, J=7.1Hz), 1.80-2.00 (2H, m), 2.48-2.62 (6H, m), 2.78 (2H, t, J=6.2Hz), 4.37 (1H, d, J=24.4Hz), 4.76 (2H, s), 6.80 (1H, d, J=6.8Hz), 7.32 (1H, t, J=7.3Hz), 7.39-7.93 (20H, m)

NMR (15) ($CDCl_3$) δppm: 1.72-2.05 (2H, m), 2.30-2.57 (4H, m), 2.70-2.89 (2H, m), 3.54-3.83 (4H, m), 4.37 (1H, d, J=28.0Hz), 4.74 (2H, s), 6.77 (1H, d, J=8.3Hz), 7.33 (1H, t, J=7.3Hz), 7.40-7.96 (20H, m)

NMR (16) ($CDCl_3$) δppm: 1.81-2.01 (2H, m), 2.22 (3H, s), 2.28-2.68 (10H, m), 2.79 (2H, t, J=6.9Hz), 4.37 (1H, d, J=24.0Hz), 4.76 (2H, s), 6.79 (1H, d, J=8.4Hz), 7.33 (1H, t, J=8.8Hz), 7.40-7.64 (10H, m), 7.64-7.95 (10H, m)

NMR (17) ($CDCl_3$) δppm: 1.7-3.3 (16H, m), 3.59 (2H, m), 4.81 (2H, s), 6.82 (1H, d, J=8.5Hz), 7.2-8.0 (21H, m)

NMR (18) ($CDCl_3$) δppm: 1.4-1.7 (2H, m), 1.75-2.0 (4H, m), 2.2-2.4 (2H, m), 2.4-2.6 (2H, m), 2.65-2.9 (4H, m), 3.65 (1H, m), 4.1-4.8 (2H, br), 4.68 (2H, s), 6.70 (1H, d, J=8.5Hz), 7.2-7.9 (21H, m)

NMR (19) ($CDCl_3$) δppm: 1.41-2.31 (9H, m), 2.24 (6H, s), 2.46 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7.5Hz), 2.93-3.12 (2H, m), 4.23-4.60 (1H, br), 4.73 (2H, s), 6.75 (1H, d, J=8.5Hz), 7.23-7.92 (21H, m)

NMR (20) ($CDCl_3$) δppm: 1.48-2.28 (9H, m), 2.36-2.61 (6H, m), 2.77 (2H, t, J=7.5Hz), 2.92-3.13 (2H, m), 3.65 (4H, t, J=4.5Hz), 4.19-4.58 (1H, m), 4.70 (2H,

s), 6.71 (1H, d, J=8.5Hz), 7.02-7.94 (21H, m)

NMR (21) ($CDCl_3$) δppm: 1.41-2.03 (8H, m), 2.05-2.80 (13H, m), 2.77 (2H, t, J=7.6Hz), 2.88-3.07 (2H, m), 4.73 (2H, s), 6.75 (1H, d, J=8.5Hz), 7.32 (1H, t, J=6.4Hz), 7.40-7.90 (20H, m)

NMR (22) ($CDCl_3$) δppm: 1.62-2.23 (8H, m), 2.29-2.97 (12H, m), 3.48-3.93 (3H, m), 4.22-4.57 (1H, br), 4.69 (2H, s), 6.70 (1H, d, J=8.5Hz), 7.22-8.04 (21H, m)

NMR (23) ($CDCl_3$) δppm: 1.69-2.00 (3H, m), 2.00-2.62 (16H, m), 2.62-2.87 (4H, m), 3.50-3.92 (3H, m), 4.37 (1H, d, J=26.8Hz), 4.75 (2H, s), 6.77 (1H, d, J=8.4Hz), 7.28-7.92 (21H, m)

NMR (24) ($CDCl_3$) δppm: 1.82-2.22 (4H, m), 2.50 (3H, s), 2.54-3.12 (12H, m), 4.73 (2H, s), 6.71 (1H, d, J=8.6Hz), 7.29-7.88 (21H, m)

NMR (25) ($CDCl_3$) δppm: 1.55-1.85 (4H, m), 2.3-2.5 (6H, m), 2.7-2.9 (2H, m), 3.67 (4H, t, J=4.5Hz), 4.25-4.55 (2H, m), 4.76 (2H, s), 6.78 (1H, d, J=8.5Hz), 7.25-7.95 (21H, m)

NMR (26) (DMSO-d_6) δppm: 1.37-1.70 (4H, m), 2.08 (3H, s), 2.14-2.43 (10H, m), 2.60-2.77 (2H, m), 4.33 (1H, d, J=26.0Hz), 4.96 (2H, s), 6.80 (1H, d, J=10.0Hz), 7.27-7.38 (1H, m), 7.38-7.80 (19H, m), 7.90-8.03 (1H, m)

NMR (27) ($CDCl_3$) δppm: 1.00 (3H, t, J=7.0Hz), 1.01 (3H, t, J=7.0Hz), 2.68 (2H, t, J=6.9Hz), 3.12-3.27 (4H, m), 3.35-3.46 (2H, m), 4.25-4.60 (1H, m), 4.96 (2H, s), 6.67 (1H, d, J=8.5Hz), 7.23-7.27 (1H, m), 7.29-7.57 (10H, m), 7.68-7.81 (9H, m), 7.92 (1H, brs), 11.97 (1H, brs)

NMR (28) ($CDCl_3$) δppm: 2.14-2.39 (4H, m), 2.22 (3H, s), 2.74 (2H, t,

J=6.3Hz), 2.98-3.20 (2H, m), 3.29-3.48 (2H, m), 3.63-3.80 (2H, m), 4.17-4.54 (1H, m), 4.73 (2H, s), 6.67 (1H, d, J=8.6Hz), 7.26-7.33 (1H, m), 7.33-7.62 (10H, m), 7.62-7.85 (9H, m), 7.90 (1H, brs)

NMR (29) ($CDCl_3$) δppm: 0.89 (3H, t, J=7.1Hz), 1.00 (3H, t, J=7.1Hz), 2.35-4.47 (15H, m), 4.73 (2H, s), 6.67-6.74 (1H, m), 7.20-7.61 (11H, m), 7.61-7.85 (9H, m), 7.85-7.93 (1H, m)

NMR (30) ($CDCl_3$) δppm: 1.01-1.47 (2H, m), 1.65-1.90 (2H, m), 2.29 (3H, s), 2.35-2.65 (11H, m), 2.65-2.91 (2H, m), 3.03-3.22 (2H, m), 3.73-3.91 (1H, m), 4.22-4.54 (1H, m), 4.73 (2H, s), 4.75-4.92 (1H, m), 6.69 (1H, d, J=8.6Hz), 7.22-7.63 (11H, m), 7.63-7.88 (9H, m), 7.88-8.00 (1H, m)

NMR (31) ($CDCl_3$) δppm: 2.18-3.50 (20H, m), 3.50-3.71 (1H, m), 3.71-3.95 (1H, m), 4.20-4.82 (4H, m), 6.65-6.74 (1H, m), 7.20-7.63 (12H, m), 7.63-7.86 (9H, m), 7.86-7.98 (1H, m)

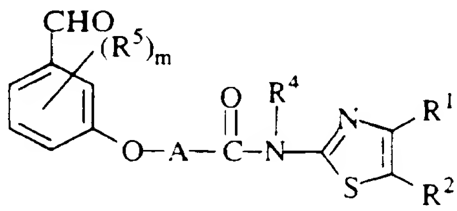
NMR (32) ($CDCl_3$) δppm: 4.09 (3H, s), 4.42 (1H, d, J=22.9Hz), 4.85 (2H, s), 6.93 (1H, d, J=8.7Hz), 7.00-7.18 (1H, m), 7.18-7.98 (18H, m), 8.19 (1H, dd, J=2.2Hz, J=8.7Hz), 8.60 (1H, d, J=2.2Hz), 11.55 (1H, br)

NMR (33) ($CDCl_3$) δppm: 2.73 (2H, t, J=7.4Hz), 3.37 (2H, t, J=7.4Hz), 4.06 (1H, d, J=20.6Hz), 4.84 (2H, s), 6.77 (1H, d, J=8.6Hz), 7.28-7.77 (20H, m), 10.85 (1H, br), 12.16 (1H, br)

NMR (35) (DMSO-d_6) δppm: 2.03-2.46 (2H, m), 2.67-3.06 (2H, m), 4.28-4.52 (1H, m), 4.94-5.24 (1H, m), 6.83-8.11 (22H, m), 12.61 (1H, brs)

Using the suitable starting compounds, the compounds as listed in Tables 23-31 are obtained in the same manner as in Reference Example 2.

Table 23



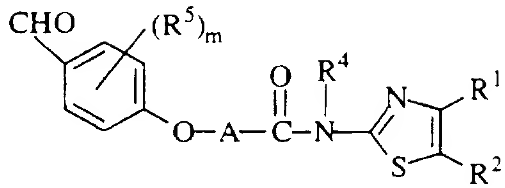
Reference Example 105

R1: H	R^2: H	R^4:H
R^5: H	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (1)

[1]H-NMR spectrum (NMR (1)) as described in Table 23 are as follows:

NMR (1) ($CDCl_3$) δppm: 4.81 (2H, s), 7.05 (1H, d, J=3.5Hz), 7.25-7.35 (2H, m), 7.45-7.65 (2H, m), 7.50 (1H, d, J=3.5Hz), 10.00 (1H, s), 10.06 (1H, brs)

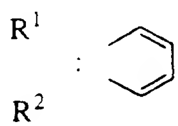
Table 24



Reference Example 106

R^1: H	R^2: H	R^4:H
R^5: H	m: 1	A: $-(CH_2)_3-$
Crystalline form: Pale yellow particles	Form: Free	NMR (1)

Reference Example 107



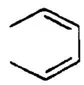
	R^5: H	R^4: H
	m: 1	A: $-CH_2-$
Crystalline form: Pale yellow particles	Form: Free	NMR (2)

Reference Example 108

R^1: H	R^2: H	R^4:H
R^5: CH_3 (2- and 6-positions)	m: 2	A: $-CH_2-$
Crystalline form: Yellow powder	Form: Free	NMR (3)

Table 25

Reference Example 109

R^1
: 
R^2

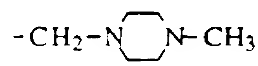
R^5: $-CH_2N(C_2H_5)_2$ (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: White powder Form: Free NMR (4)

Reference Example 110

R^1
: 
R^2

R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow powder Form: Free NMR (5)

Reference Example 111

R^1
: 
R^2

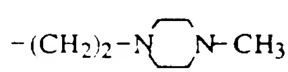
R^5: $-(CH_2)_2N(C_2H_5)_2$ (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Brown powder Form: HCl NMR (6)

Reference Example 112

R^1
: 
R^2

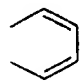
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: White powder Form: 2HCl NMR (7)

Table 26

Reference Example 113

R^1 :  R^2

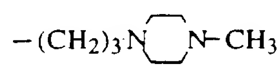
R^5: $-(CH_2)_3OH$ (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: White powder Form: Free NMR (8)

Reference Example 114

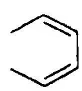
R^1 :  R^2

R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Pale yellow powder Form: Free NMR (9)

Reference Example 115

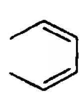
R^1 :  R^2

R^5: $-CH_2N(C_2H_5)_2$ (2-position)

R^4: H m: 1 A: $-(CH_2)_5-$

Crystalline form: Yellow oil Form: Free NMR (10)

Reference Example 116

R^1 :  R^2

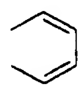
R^5: $-CH_2N(C_2H_5)_2$ (2-position)

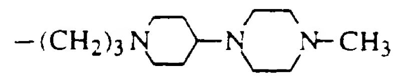
R^4: H m: 1 A: $-(CH_2)_3-$

Crystalline form: Yellow amorphous Form: Free NMR (11)

Table 27

Reference Example 117

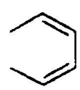
R^1 : 
R^2

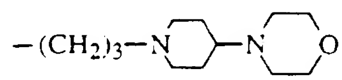
R^5:  (2-position)

R^4: H   m: 1   A: $-CH_2-$

Crystalline form: Pale yellow powder   Form: Free   NMR (12)

Reference Example 118

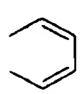
R^1 : 
R^2

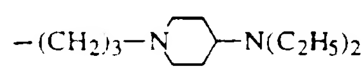
R^5:  (2-position)

R^4: H   m: 1   A: $-CH_2-$

Crystalline form: Yellow powder   Form: 2HCl   NMR (13)

Reference Example 119

R^1 : 
R^2

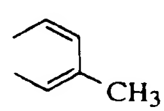
R^5:  (2-position)

R^4: H   m: 1   A: $-CH_2-$

Crystalline form: Pale yellow powder   Form: 2HCl   NMR (14)

Reference Example 120

R^1 R^5: H R^4: H

: 

R^2 m: 1   A: $-CH_2-$

Crystalline form: Yellow powder   Form: Free   NMR (15)

Table 28

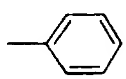
Reference Example 121

R^1: CH_3	R^2: H	R^4:H
R^5: H	m: 1	A: $-CH_2-$
Crystalline form: Pale brown powder	Form: Free	NMR (16)

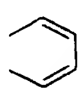
Reference Example 122

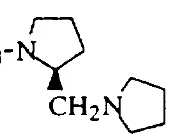
R^1: $(CH_3)_3C-$	R^2: H	R^4:H
R^5: H	m: 1	A: $-CH_2-$
Crystalline form: White powder	Form: Free	NMR (17)

Reference Example 123

R^1: 	R^2: H	R^4:H
R^5: H	m: 1	A: $-CH_2-$
Crystalline form: Pale yellow powder	Form: Free	NMR (18)

Reference Example 124

R^1 / R^2 : 

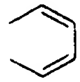
R^5: $-(CH_2)_3-$ 

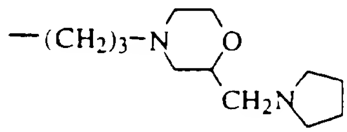
(2-position)

R^4: H	m: 1	A: $-CH_2-$
Crystalline form: Pale yellow oil	Form: Free	NMR (19)

Table 29

Reference Example 125

R^1 / R^2 : 

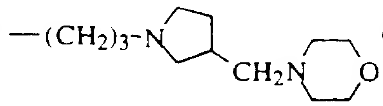
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: Free NMR (20)

Reference Example 126

R^1 / R^2 : 

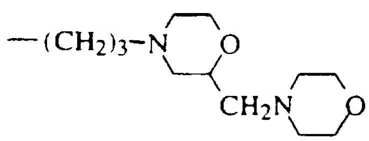
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: Free NMR (21)

Reference Example 127

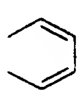
R^1 / R^2 : 

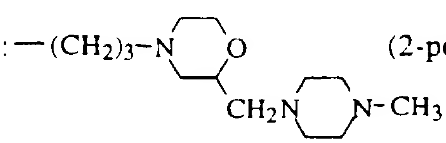
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: Free NMR (22)

Reference Example 128

R^1 / R^2 : 

R^5:  (2-position)

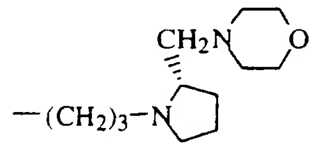
R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: Free NMR (23)

Table 30

Reference Example 129

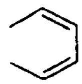
R^1 :  R^2

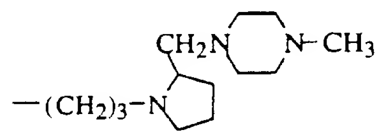
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Pale yellow amorphous Form: Free NMR (24)

Reference Example 130

R^1 :  R^2

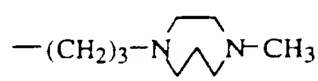
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Pale yellow amorphous Form: Free NMR (25)

Reference Example 131

R^1 :  R^2

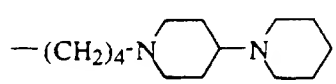
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Pale yellow amorphous Form: Free NMR (26)

Reference Example 132

R^1 :  R^2

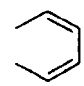
R^5:  (2-position)

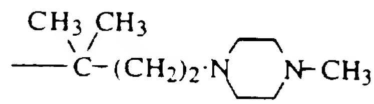
R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: 3HCl NMR (27)

Table 31

Reference Example 133

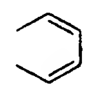
R^1
: 
R^2

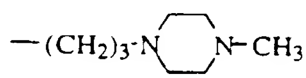
R^5:  (2-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Yellow amorphous Form: Free NMR (28)

Reference Example 134

R^1
: 
R^2

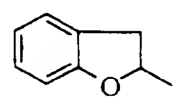
R^5:  (3-position)

R^4: H m: 1 A: $-CH_2-$

Crystalline form: Colorless amorphous Form: Free NMR (29)

Reference Example 135

R^1
: 
R^2

R^5 and A combine to form : 

R^4: H m: 1

Crystalline form: White oil Form: Free NMR (30)

^{1}H-NMR spectrum (NMR (1) to NMR (30)) as described in Tables 24-31 are as follows:

NMR (1) (DMSO-d_6) δppm: 2.08 (2H, q, J=6.6Hz), 2.62 (2H, t, J=7.2Hz), 4.13 (2H, t, J=4.1Hz), 7.10 (2H, d, J=8.6Hz), 7.19 (1H, d, J=3.6Hz), 7.45 (1H, d, J=3.6Hz), 7.85 (2H, d, J=8.6Hz), 9.86 (1H, s), 12.13 (1H, s)

NMR (2) (DMSO-d_6) δppm: 5.07 (2H, s), 7.19 (2H, d, J=8.7Hz), 7.27-7.40 (1H, m), 7.40-7.56 (1H, m), 7.77 (1H, d, J=7.5Hz), 7.90 (2H, d, J=8.8Hz), 7.98 (1H, d, J=7.1Hz), 9.89 (1H, s), 12.1-13.0 (1H, br)

NMR (3) ($CDCl_3$) δppm: 2.38 (6H, s), 4.57 (2H, s), 7.06 (1H, d, J=3.6Hz), 7.51 (1H, d, J=3.6Hz), 7.61 (2H, s), 9.92 (1H, s), 10.10 (1H, brs)

NMR (4) ($CDCl_3$) δppm: 1.13 (6H, t, J=7.1Hz), 2.93 (4H, q, J=7.1Hz), 3.79 (2H, s), 5.01 (2H, s), 7.08 (1H, d, J=8.2Hz), 7.23-7.35 (1H, m), 7.35-7.45 (1H, m), 7.74-7.87 (4H, m), 9.92 (1H, s), 10.71 (1H, s)

NMR (5) ($CDCl_3$) δppm: 2.33 (3H, s), 2.42-2.88 (8H, m), 3.71 (2H, s), 4.92 (2H, s), 7.02 (1H, d, J=8.2Hz), 7.27-7.40 (1H, m), 7.40-7.59 (1H, m), 7.67-7.93 (1H, m), 9.93 (1H, s)

NMR (6) ($CDCl_3$) δppm: 1.29 (6H, t, J=7.1Hz), 2.98-3.48 (8H, m), 5.20 (2H, s), 7.22 (1H, d, J=9.0Hz), 7.35 (1H, d, J=7.6Hz), 7.49 (1H, d, J=7.6Hz), 7.80 (1H, d, J=7.8Hz), 7.85 -7.98 (2H, m), 8.01 (1H, d, J=7.4Hz), 9.91 (1H, s), 10.36 (1H, br), 12.84 (1H, br)

NMR (7) ($CDCl_3$) δppm: 2.86 (3H, s), 3.14-4.00 (12H, m), 5.21 (2H, s), 7.22 (1H, d, J=7.8Hz), 7.35 (1H, t, J=7.6Hz), 7.49 (1H, t, J=7.6Hz), 7.78-7.87 (3H, m), 8.01 (1H, d, J=8.1Hz), 9.90 (1H, s), 11.60 (2H, br), 12.75 (1H, br)

NMR (8) ($CDCl_3$) δppm: 1.83-2.11 (2H, m), 3.06 (2H, t, J=7.3Hz), 3.85 (2H, t, J=5.2Hz), 4.22 (1H, br), 4.85 (2H, s), 6.98 (1H, d, J=8.2Hz), 7.28-7.41 (1H, m), 7.41-7.49 (1H, m), 7.74-7.86 (4H, m), 9.92 (1H, s), 11.84 (1H, br)

NMR (9) ($CDCl_3$) δppm: 1.83-2.06 (2H, m), 2.25 (3H, s), 2.32-2.76 (10H, m), 2.88 (2H, t, J=7.7Hz), 4.87 (2H, s), 6.97 (1H, d, J=8.3Hz), 7.30-7.42 (1H, m), 7.42-7.51 (1H, m), 7.72-7.87 (4H, m), 9.94 (1H, s)

NMR (10) ($CDCl_3$) δppm: 0.99 (6H, t, J=7.1Hz), 1.40-1.61 (2H, m), 1.70-1.92 (4H, m), 2.43-2.63 (6H, m), 3.56 (2H, s), 3.95 (2H, t, J=6.3Hz), 6.86 (1H, d, J=8.5Hz), 7.28-7.40 (1H, m), 7.40-7.51 (1H, m), 7.70-7.91 (3H, m), 7.95 (1H, d, J=2.1Hz), 9.89 (1H, s). 10.39-13.00 (1H, brs)

NMR (11) ($CDCl_3$) δppm: 0.97 (6H, t, J=7.1Hz), 2.10-2.40 (2H, m), 2.40-2.68 (6H, m), 3.54 (2H, s), 3.95-4.23 (2H, m), 6.84 (1H, t, J=8.5Hz), 7.20-7.40 (2H, m), 7.58-7.88 (3H, m), 7.90 (1H, d, J=2.1Hz), 9.87 (1H, s)

NMR (12) ($CDCl_3$) δppm: 1.38-1.76 (2H, m), 1.76-2.13 (6H, m), 2.13-2.70 (14H, m), 2.88 (2H, t, J=7.6Hz), 2.95-3.18 (2H, m), 4.86 (2H, s), 6.97 (1H, d, J=8.2Hz), 7.31-7.42 (1H, m), 7.42-7.57 (1H, m), 7.73-7.87 (4H, m), 9.91 (1H, s)

NMR (13) (DMSO-d_6) δppm: 1.92-2.45 (6H, m), 2.60-3.21 (9H, m), 3.21-3.76 (4H, m), 3.76-4.16 (4H, m), 5.17 (2H, s), 7.15 (1H, d, J=8.8Hz), 7.31 (1H, t, J=6.9Hz), 7.45 (1H, t, J=6.9Hz), 7.68-7.92 (3H, m), 7.99 (1H, d, J=7.0Hz), 9.87 (1H, s), 10.73 (1H, br), 11.78 (1H, br), 12.80 (1H, s)

NMR (14) (DMSO-d_6) δppm: 1.28 (6H, t, J=7.1Hz), 2.00-2.38 (6H, m), 2.68-2.90 (2H, m), 2.90-3.25 (8H, m), 3.47-3.83 (3H, m), 5.18 (2H, s), 7.18 (1H, d, J=8.7Hz), 7.34 (1H, t, J=7.7Hz), 7.45 (1H, t, J=7.7Hz), 7.78-7.86 (3H, m), 8.00 (1H, d, J=7.0Hz), 9.90 (1H, s), 10.78 (2H, br), 12.80 (1H, br)

NMR (15) (DMSO-d_6) δppm: 2.40 (3H, s), 5.06 (2H, s), 7.15-7.40 (3H, m), 7.65 (1H, d, J=8.4Hz), 7.77 (1H, s), 7.89 (2H, d, J=8.6Hz), 9.88 (1H, s), 12.61 (1H, s)

NMR (16) (DMSO-d_6) δppm: 2.27 (3H, d, J=0.9Hz), 4.98 (2H, s), 6.79 (1H, d, J=1.0Hz), 7.12-7.25 (2H, m), 7.82-7.96 (2H, m), 9.88 (1H, s), 12.0-12.7 (1H, br)

NMR (17) (DMSO-d_6) δppm: 1.26 (9H, s), 4.98 (2H, s), 6.78 (1H, s), 7.15 (2H, d, J=8.8Hz), 7.90 (2H, d, J=8.8Hz), 9.88 (1H, s), 12.42 (1H, s)

NMR (18) (DMSO-d_6) δppm: 5.05 (2H, s), 7.19 (2H, d, J=8.8Hz), 7.25-7.55 (3H, m), 7.69 (1H, s), 7.80-8.02 (4H, m), 9.89 (1H, s), 12.60 (1H, s)

NMR (19) (DMSO-d_6) δppm: 1.57-1.84 (7H, m), 1.84-2.05 (3H, m), 2.20 (1H, q, J=8.5Hz), 2.30-2.72 (8H, m), 2.74-3.12 (3H, m), 3.16-3.30 (1H, m), 4.87 (2H, s), 6.97 (1H, d, J=8.3Hz), 7.27-7.41 (1H, m), 7.41-7.53 (1H, m), 7.70-7.93 (4H, m), 9.91 (1H, s)

NMR (20) ($CDCl_3$) δppm: 1.67-2.95 (20H, m), 3.55-3.95 (3H, m), 4.90 (2H, s), 6.96 (1H, d, J=8.3Hz), 7.25-7.53 (2H, m), 7.55-7.95 (4H, m), 9.90 (1H, s)

NMR (21) ($CDCl_3$) δppm: 1.55-3.80 (23H, m), 4.91 (2H, s). 6.96 (1H, d, J=8.4Hz), 7.25-7.52 (2H, m), 7.65-7.78 (4H, m), 9.88 (1H, s)

NMR (22) ($CDCl_3$) δppm: 1.75-2.95 (16H, m), 3.55-3.95 (7H, m), 4.88 (2H, s), 6.95 (1H, d, J=8.3Hz) 7.28-7.55 (2H, m), 7.65-7.95 (4H, m), 9.90 (1H, s)

NMR (23) ($CDCl_3$) δppm: 1.75-3.00 (20H, m), 2.27 (3H, s), 3.58-3.98 (3H, m), 4.88 (2H, s), 6.95 (1H, d, J=8.3Hz), 7.30-7.52 (2H, m), 7.65-7.90 (4H, m), 9.89 (1H, s)

NMR (24) ($CDCl_3$) δppm: 1.5-3.4 (15H, m), 2.40 (4H, t, J=4.5Hz), 3.61

(4H, t, J=4.5Hz), 4.88 (2H, s), 6.99 (1H, d, J=8.5Hz), 7.3-7.55 (2H, m), 7.7-7.9 (4H, m), 9.92 (1H, s)

NMR (25) ($CDCl_3$) δppm: 1.5-3.1 (23H, m), 2.24 (3H, s), 4.91 (2H, s), 7.00 (1H, d, J=8Hz), 7.3-7.5 (2H, m), 7.7-7.9 (4H, m), 9.91 (1H, s)

NMR (26) ($CDCl_3$) δppm: 1.7-2.0 (4H, m), 2.33 (3H, s), 2.5-3.0 (12H, m), 4.87 (2H, s), 6.97 (1H, d, J=8Hz), 7.3-7.9 (6H, m), 9.91 (1H, s)

NMR (27) (DMSO-d_6) δppm: 1.30-3.51 (25H, m), 3.51-3.75 (2H, m), 5.16 (2H, s), 7.09 (1H, d, J=8.9Hz), 7.27-7.39 (1H, m), 7.39-7.52 (1H, m), 7.70-7.84 (3H, m), 7.98-8.09 (1H, m), 9.86 (1H, s), 10.58-11.17 (3H, m)

NMR (28) (DMSO-d_6) δppm: 1.45 (6H, s), 2.68-3.01 (2H, m), 2.77 (3H, s), 3.21-3.85 (10H, m), 5.24 (2H, s), 7.10 (1H, d, J=8.3Hz), 7.29-7.40 (1H, m), 7.40-7.52 (1H, m), 7.74-7.89 (3H, m), 7.93-8.05 (1H, m), 9.89 (1H, s), 11.10-13.00 (3H, m)

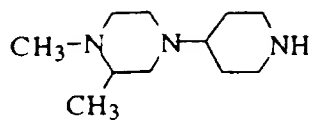
NMR (29) ($CDCl_3$) δppm: 1.86 (2H, quint, J=7.5Hz), 2.18-2.63 (10H, m), 2.30 (3H, s), 3.05 (2H, t, J=7.5Hz), 4.82 (2H, s), 6.24-7.01 (2H, m), 7.10-7.59 (3H, m), 7.73-7.93 (3H, m), 10.17 (1H, s)

NMR (30) ($CDCl_3$) δppm: 3.46 (1H, dd, J=6.5Hz, J=16.5Hz), 3.68 (1H, dd, J=10.5Hz, J=16.5Hz), 5.67 (1H, dd, J=6.5Hz, J=10.5Hz), 7.08 (1H, d, J=8.5Hz), 7.25-7.55 (2H, m), 7.75-7.85 (3H, m), 7.99 (2H, d, J=8.5Hz), 9.84 (1H, s)

Using the suitable starting compounds, the compounds as listed in Tables 32-37 are obt[illegible] in the same manner as in Reference Examples 7, 8 or 9.

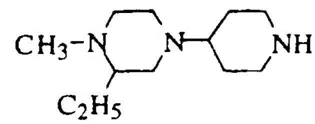
Table 32

Reference Example 136



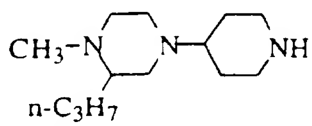
B.p.: 145°C (0.3 mmHg)
Crystalline form: Colorless oil
Form: Free
NMR (1)

Reference Example 137



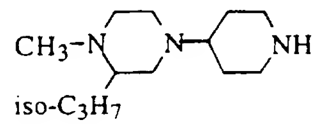
Crystalline form: Pale yellow oil
Form: Free
NMR (2)

Reference Example 138



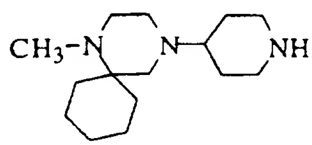
Crystalline form: Colorless oil
Form: Free
NMR (3)

Reference Example 139



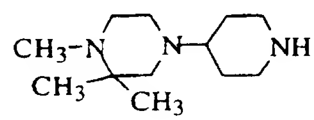
Crystalline form: Brown oil
Form: Free
NMR (4)

Reference Example 140



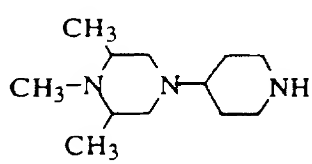
Crystalline form: Brown oil
Form: Free
NMR (5)

Reference Example 141



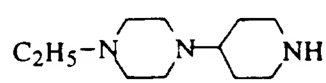
B.p.: 90-95°C (0.15 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 142



(cis-form)
B.p.: 90-95°C (0.2 mmHg)
Crystalline form: Colorless oil
Form: Free

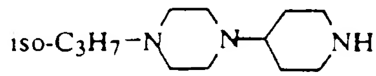
Reference Example 143



B.p.: 107°C (0.35 mmHg)
Crystalline form: Colorless oil
Form: Free

Table 33

Reference Example 144

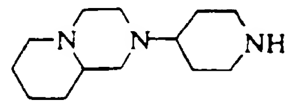


Crystalline form: White solid

Form: Free

NMR (6)

Reference Example 145

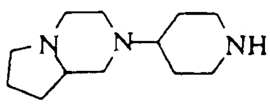


B.p.: 160-165°C (0.25-0.3 mmHg)

Crystalline form: Colorless oil

Form: Free

Reference Example 146



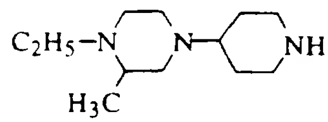
B.p.: 135-140°C (0.25-0.3 mmHg)

Crystalline form: Colorless oil

Form: Free

NMR (7)

Reference Example 147

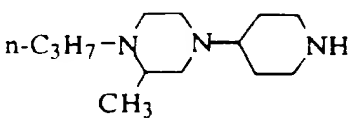


Crystalline form: Colorless oil

Form: Free

NMR (8)

Reference Example 148

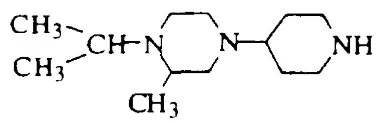


Crystalline form: Colorless oil

Form: Free

NMR (9)

Reference Example 149

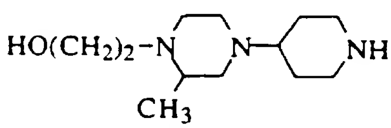


Crystalline form: White amorphous

Form: Free

NMR (10)

Reference Example 150

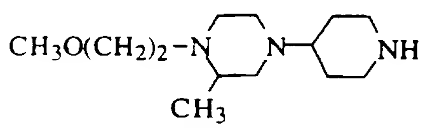


Crystalline form: Colorless oil

Form: Free

NMR (11)

Reference Example 151



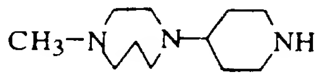
Crystalline form: Brown oil

Form: Free

NMR (12)

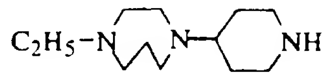
Table 34

Reference Example 152



B.p.: 110-115°C (0.22 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 153

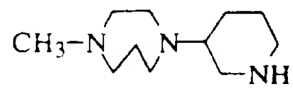


Crystalline form: Pale yellow oil
Form: Free
NMR (13)

Reference Example 154

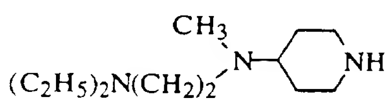
Crystalline form:Yellow powder
Form: Free
NMR (14)

Reference Example 155



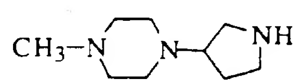
B.p.: 110°C (0.35 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 156



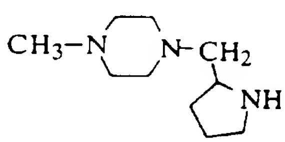
B.p.: 110-115°C (0.28 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 157



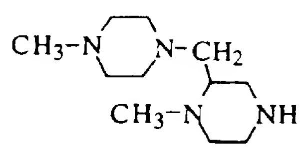
B.p.: 120-127°C (12 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 158



B.p.: 113-130°C (18 mmHg)
Crystalline form: Colorless oil
Form: Free

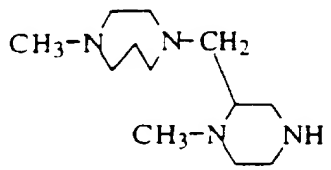
Reference Example 159



B.p.: 165-170°C (15 mmHg)
Crystalline form: Colorless oil
Form: Free
NMR (15)

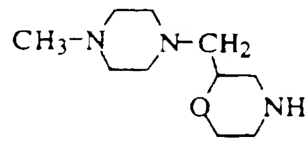
Table 35

Reference Example 160



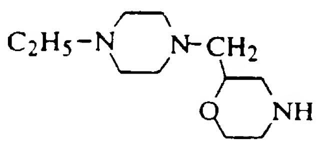
B.p.: 180-185°C (15 mmHg)
Crystalline form: Colorless oil
Form: Free
NMR (16)

Reference Example 161



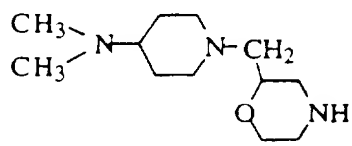
B.p.: 138-143°C (12 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 162



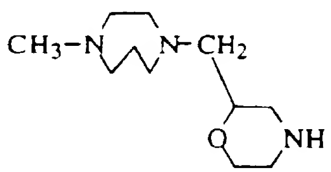
B.p.: 112-116°C (0.23 mmHg)
M.p. 39-41°C
Crystalline form: Colorless oil
Form: Free

Reference Example 163



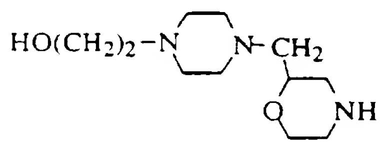
B.p.: 116°C (0.23 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 164



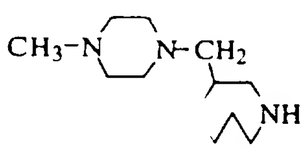
B.p.: 108°C (0.3 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 165



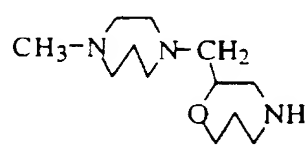
M.p. 73-75.5°C
Crystalline form: White powder
Form: Free

Reference Example 166



B.p.: 134-137°C (2.5 mmHg)
Crystalline form: Colorless oil
Form: Free

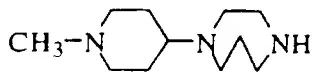
Reference Example 167



B.p.: 124-130°C (0.7 mmHg)
Crystalline form: Colorless oil
Form: Free

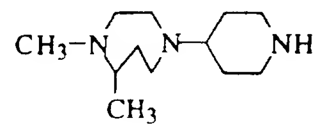
Table 36

Reference Example 168



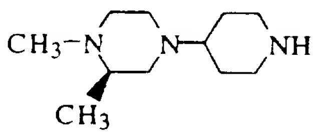
Crystalline form: White powder
Form: 3HCl
NMR (17)

Reference Example 169



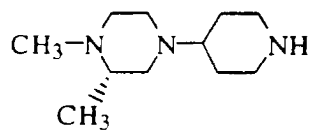
Form: Free
NMR (18)

Reference Example 170



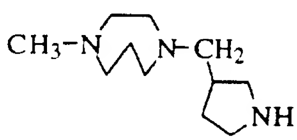
Crystalline form: Colorless oil
Form: Free
NMR (19)

Reference Example 171



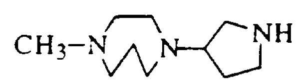
Crystalline form: Colorless oil
Form: Free
NMR (20)

Reference Example 172



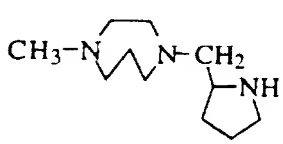
B.p.: 110-128°C (20 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 173



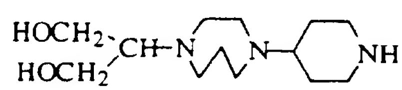
B.p.: 115-136°C (20 mmHg)
Crystalline form: Colorless oil
Form: Free

Reference Example 174



B.p.: 115-133°C (20 mmHg)
Crystalline form: Colorless oil
Form: Free

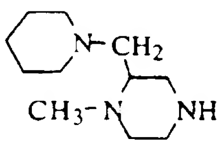
Reference Example 175



Crystalline form: White powder
Form: 3HCl
NMR (21)

Table 37

Reference Example 176



B.p.: 165-170°C (18 mmHg)
Crystalline form: Yellow oil
Form: Free
NMR (22)

[1]H-NMR spectrum (NMR (1) to NMR (22)) as described in Tables 32-37 are as follows:

NMR (1) ($CDCl_3$) δppm: 1.05 (3H, d, J=6Hz), 1.25-1.55 (2H, m), 1.75-3.3 (14H, m), 2.31 (3H, s)

NMR (2) ($CDCl_3$) δppm: 0.89 (3H, t, J=7.5Hz), 1.17-1.54 (3H, m), 1.54-1.78 (1H, m), 1.78-1.94 (2H, m), 1.94-2.18 (3H, m), 2.18-2.49 (6H, m), 2.49-2.72 (2H, m), 2.72-2.95 (3H, m), 3.03-3.27 (2H, m)

NMR (3) ($CDCl_3$) δppm: 0.91 (3H, t, J=7Hz), 1.15-1.7 (5H, m), 1.75-2.15 (6H, m), 2.28 (3H, s), 2.15-2.45 (3H, m), 2.45-2.65 (2H, m), 2.7-2.95 (3H, m), 3.05-3.25 (2H, m)

NMR (4) ($CDCl_3$) δppm: 0.85-0.94 (6H, m), 1.23-1.54 (2H, m), 1.62 (1H, br), 1.80-1.96 (3H, m), 1.96-2.18 (2H, m), 2.18-2.45 (6H, m), 2.45-2.68 (2H, m), 2.68-2.92 (3H, m), 3.00-3.24 (2H, m)

NMR (5) ($CDCl_3$) δppm: 1.06-1.98 (15H, m), 2.20-2.47 (5H, m), 2.47-2.61 (1H, m), 2.61-2.90 (6H, m), 3.09-3.33 (2H, m)

NMR (6) ($CDCl_3$) δppm: 1.06 (6H, d, J=6.5Hz), 1.25-1.55 (2H, m), 1.75-1.95 (2H, m), 2.2-2.4 (1H, m), 2.45-2.75 (11H, m), 3.05-3.2 (2H, m)

NMR (7) ($CDCl_3$) δppm: 1.25-1.6 (3H, m), 1.6-2.75 (14H, m), 2.85 (1H, dd,

J=2Hz, J=11.5Hz), 2.9-3.3 (5H, m)

NMR (8) ($CDCl_3$) δppm: 1.00 (3H, t, J=7.3Hz), 1.04 (3H, d, J=6.3Hz), 1.24-1.51 (2H, m), 1.70-1.92 (3H, m), 2.03 (1H, t, J=10.7Hz), 2.20-2.50 (5H, m), 2.50-2.69 (2H, m), 2.69-3.00 (4H, m), 3.07-3.22 (2H, m)

NMR (9) ($CDCl_3$) δppm: 0.84 (3H, t, J=7.3Hz), 1.03 (3H, d, J=6.2Hz), 1.25-1.65 (4H, m), 1.65-1.93 (3H, m), 2.02 (1H, q, J=10.7Hz), 2.19-2.48 (5H, m), 2.48-2.95 (6H, m), 3.05-3.21 (2H, m)

NMR (10) ($CDCl_3$) δppm: 0.89 (3H, d, J=6.5Hz), 1.03 (6H, dd, J=6.5Hz, J=15.1Hz), 1.44-1.69 (2H, m), 1.80-2.00 (2H, m), 2.05-2.24 (2H, m), 2.24-2.50 (2H, m), 2.50-2.95 (6H, m), 3.13-3.40 (3H, m), 4.85 (1H, br)

NMR (11) ($CDCl_3$) δppm: 1.03 (3H, d, J=6.2Hz), 1.33-1.52 (2H, m), 1.72-3.08 (16H, m), 3.08-3.23 (2H, m), 3.45-3.80 (2H, m)

NMR (12) ($CDCl_3$) δppm: 1.04 (3H, d, J=6.2Hz), 1.49-1.68 (2H, m), 1.80-1.99 (2H, m), 2.06 (1H, t, J=10.1Hz), 2.24-2.55 (5H, m), 2.57-2.88 (4H, m), 2.90-3.10 (2H, m), 3.15-3.31 (3H, m), 3.34 (3H, s), 3.44-3.62 (2H, m)

NMR (13) ($CDCl_3$) δppm: 1.07 (3H, t, J=7.1Hz), 1.40 (2H, dq, J=3.8Hz, J=12.0Hz), 1.65-1.98 (5H, m), 2.39-2.72 (9H, m), 2.72-2.84 (4H, m), 3.05-3.22 (2H, m)

NMR (14) ($CDCl_3$) δppm: 0.91 (3H, t, J=7.1Hz), 1.14-1.58 (5H, m), 1.58-2.13 (5H, m), 2.22-2.87 (13H, m), 3.01-3.24 (2H, m)

NMR (15) ($CDCl_3$) δppm: 2.0-3.2 (17H, m), 2.26 (3H, s), 2.32 (3H, s)

NMR (16) ($CDCl_3$) δppm: 1.8-1.9 (2H, m), 2.0-3.2 (17H, m), 2.33 (3H, s), 2.34 (3H, s)

NMR (17) ($DMSO-d_6$) δppm: 1.94-2.46 (6H, m), 2.69 (3H, d, J=3.7Hz), 2.84-3.16 (2H, m), 3.16-4.30 (11H, m), 9.56 (1H, br), 9.99 (1H, br), 11.04 (1H, br), 12.06 (1H, br)

NMR (18) ($CDCl_3$) δppm: 1.08 (3H, d, J=6.2Hz), 1.28-1.55 (2H, m), 1.55-1.95 (5H, m), 2.38 (3H, s), 2.40-2.99 (10H, m), 3.02-3.22 (2H, m)

NMR (19) ($CDCl_3$) δppm: 1.05 (3H, d, J=6Hz), 1.25-1.55 (2H, m), 1.75-3.3 (14H, m), 2.31 (3H, s)

NMR (20) ($CDCl_3$) δppm: 1.05 (3H, d, J=6Hz), 1.25-1.55 (2H, m), 1.75-3.3 (14H, m), 2.31 (3H, s)

NMR (21) ($DMSO-d_6$) δppm: 1.78-2.47 (6H, m), 2.68-3.06 (2H, m), 3.14-4.32 (16H, m), 5.20-5.78 (2H, m), 9.1-9.82 (2H, m), 10.54-11.36 (1H, m), 11.82-12.38 (1H, m)

NMR (22) ($CDCl_3$) δppm: 1.3-1.7 (6H, m), 2.0-3.2 (13H, m), 2.32 (3H, s)

Reference Example 182

To a solution of t-butyl propiolate (9.7 g) in tetrahydrofuran (300 ml) is added dropwise a 1.6M solution of n-butyl lithium in n-hexane (48 ml) at −70°C, and the mixture is reacted for 10 minutes. To the mixture is added dropwise a solution of 2-{(2-methoxy-4-formylphenoxy)methylcarbonylamino}-benzothiazole (10 g) in tetrahydrofuran (200 ml) and N,N-dimethylpropylene urea (20 ml) at the same temperature over a period of 20 minutes. The reaction mixture is further reacted for 20 minutes, and then the reaction vessel is taken out from the iced bath, and the mixture is further stirred for 20 minutes. To the

mixture is added acetic acid (5 ml), and the mixture is diluted with ethyl acetate. The organic layer is washed with a saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, concentrated, and the residue thus obtained is recrystallized from ethyl acetate-n-hexane. The crystals are collected by filtration to give 2-[2-methoxy-4-(3-t-butoxycarbonyl-1-hydroxypropargyl)phenoxymethylcarbonylamino]benzothiazole (13 g) as white power.

Reference Example 183

A solution of sodium hydroxide (4.92 g) in water (5 ml) is diluted with ethanol (80 ml), and the mixture is subjected to deaeration, and then put under nitrogen atmosphere. To the mixture is added 3-methoxy-4-dimethylamino-carbonylthiobenzaldehyde (20 g), and the mixture is refluxed for 14 hours. After cooling, to the mixture is added dropwise ethyl bromoacetate (9.74 ml), and the mixture is stirred at room temperature for three hours. To the mixture are added ethanol, 1.5N hydrochloric acid and water, and the mixture is extracted with chloroform. The extract is dried over sodium sulfate and concentrated, and the residue is purified by silica gel column chromatography (solvent; n-hexane:ethyl acetate = 9:1 $\rightarrow$ 5.6:1 $\rightarrow$4:1) to give 3-methoxy-4-ethoxycarbonylmethylthiobenzaldehyde (11.8 g) as white solid.

^{1}H-NMR ($CDCl_3$) δppm: 1.21 (3H, t, J=7.1Hz), 3.74 (2H, s), 3.99 (3H, s), 4.14 (2H, q, J=7.1Hz), 7.32-7.48 (3H, m), 9.92 (1H, s)

Reference Example 184

Using the suitable starting compounds, the following compound is obtained in the same manner as in Reference Example 1.

α-(2-Methoxy-4-formylphenoxymethyl)acetic acid:

Yellow powder

^{1}H-NMR (DMSO-d_6) δppm: 3.84 (3H, s), 4.82 (2H, s), 7.05 (1H, d, J=8Hz), 7.41 (1H, d, J=2Hz), 7.51 (1H, dd, J=2Hz, J=8Hz), 9.83 (1H, s), 13.14 (1H, br)

Reference Example 185

Using the suitable starting compounds, the following compounds are obtained in the same manner as in Reference Example 2.

2-(2-Methoxy-4-formylphenoxymethylcarbonylamino)benzimidazole:

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 4.06 (3H, s), 4.86 (2H, s), 7.09 (1H, d, J=8.5Hz), 7.3-7.55 (4H, m), 7.8-7.9 (2H, m), 9.91 (1H, s), 10.25 (1H, br)

2-(2-Ethoxy-4-formylphenoxymethylcarbonylamino)benzimidazole:

White powder

^{1}H-NMR ($CDCl_3$) δppm: 1.60 (3H, t, J=7.0Hz), 4.26 (2H, q, J=7.0Hz), 4.87 (2H, s), 7.11 (1H, d, J=8.3Hz), 7.30-7.49 (4H, m), 7.79-7.88 (2H, m), 9.90 (1H, s), 10.34 (1H, br)

2-[2-(Diethylaminocarbonylmethoxy)-4-formylphenoxymethylcarbonylamino]-benzimidazole:

White powder

^{1}H-NMR ($CDCl_3$) δppm: 1.16 (3H, t, J=7Hz), 1.30 (3H, t, J=7Hz), 3.35 (2H, q, J=7Hz), 3.49 (2H, q, J=7Hz), 4.92 (2H, s), 5.00 (2H, s), 7.09 (1H, d, J=8Hz), 7.25-7.55 (4H, m), 7.7-7.85 (2H, m), 9.86 (1H, s)

Reference Example 186

Using the suitable starting compounds, the following compounds are obtained in the same manner in Reference Example 5.

[3-(2-Chloroethyl)-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]methyl-triphenylphosphonium bromide:

^{1}H-NMR (DMSO-d_6) δppm: 3.16 (2H, t, J=7.0Hz), 3.92 (2H, t, J=7.0Hz), 5.18 (2H, s), 6.12 (2H, d, J=13.1Hz), 7.14 (1H, d, J=9.4Hz), 7.31 (1H, t, J=6.5Hz), 7.44 (1H, t, J=6.5Hz), 7.60-8.12 (19H, m), 12.70 (1H, br)

[3-(2,3-Diacetyloxypropyl)-4-(2-benzothiazolylaminocarbonylmethoxy)-benzoyl]methyltriphenylphosphonium chloride:

^{1}H-NMR ($CDCl_3$) δppm: 2.00 (3H, s), 2.05 (3H, s), 3.0-3.15 (2H, m), 4.0-4.35 (2H, m), 4.93, 5.05 (2H, AB-q, J=16Hz), 5.40 (1H, m), 6.1-6.6 (2H, br), 6.98 (1H, d, J=8Hz), 7.2-8.5 (21H, m)

Reference Example 187

To a solution of methyl 2,4-dihydroxybenzoate (25.1 g) in acetone (250 ml) are added methyl bromoacetate (14.9 ml) and potassium carbonate (21.7 g), and the mixture is refluxed for 3 hours. The mixture is filtered, and the filtrate is concentrated, and the residue is purified by silica gel column chromatography (solvent; n-hexane:ethyl acetate = 3:1) to give ethyl 2-(3-hydroxy-4-methoxy-carbonylphenoxy)acetate (31.5 g).

White solid

^{1}H-NMR ($CDCl_3$) δppm: 3.81 (3H, s), 3.91 (3H, s), 4.65 (2H, s), 6.39 (1H, d, J=2.6Hz), 6.45 (1H, dd, J=2.6Hz, J=8.8Hz), 7.73 (1H, d, J=8.8Hz), 10.97 (1H, s)

Reference Example 188

To ethanol (50 ml) are added 2-(2-phthalimide)methylbenzothiazole

(3.37 g) and hydrazine monohydrate (3 ml), and the mixture is refluxed for 30 minutes. After confirming that the starting compounds are consumed, the precipitated solid is removed by filtration, and the filtrate is concentrated. To the residue is added aqueous potassium carbonate solution, and the mixture is extracted with dichloromethane. The extract is dried over magnesium sulfate, and concentrated under reduced pressure to remove the solvent to give 2-aminomethylbenzothiazole (1.42 g).

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 1.83 (2H, br), 4.30 (2H, s), 7.33-7.51 (2H, m), 7.85-7.99 (2H, m)

Reference Example 189

To dichloromethane (50 ml) are added 2-hydroxymethylbenzothiazole (2 g) and triethylamine (2.5 ml), and further thereto is added methanesulfonyl chloride (1.03 ml) under ice-cooling, and the mixture is stirred at the same temperature for one hour. After the reaction is complete, the mixture is washed with hydrochloric acid, dried over magnesium sulfate, and concentrated under reduced pressure to the remove the solvent. The resulting crude product is dissolved in dimethylformamide (50 ml), and thereto is added potassium phthalimide (5.6 g). The mixture is heated with stirring at 70°C for one hour. After the reaction is complete, the reaction mixture is poured into water, and the precipitated crystals are collected by filtration. Separately, the filtrate is extracted with ethyl acetate, and the extract is concentrated under reduced pressure. The residue and the crystals obtained before are combined, and washed with n-hexane-diethyl ether to give 2-(2-phthalimide)methylbenzo-

thiazole (3.37 g).

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 5.30 (2H, s), 7.35-7.47 (2H, m), 7.74-8.02 (6H, m)

Reference Example 190

A solution of methyl p-formylbenzoate (12.33 g), malonic acid (16 g) and piperidine (1 ml) in pyridine (100 ml) is refluxed for two hours. The reaction mixture is poured into ice-water, and the precipitated white powder is collected by filtration, and washed with water, and dried to give 4-methoxycarbonyl cinnamic acid (14.7 g).

White powder

^{1}H-NMR (DMSO-d_6) δppm: 3.85 (3H, s), 6.65 (1H, d, J=16Hz), 7.63 (1H, d, J=16Hz), 7.82 (2H, d, J=8Hz), 8.01 (2H, d, J=8Hz), 12.57 (1H, br)

Reference Example 191

To a solution of 4-methoxycarbonylcinnamic acid (4.64 g) in acetic acid (300 ml) is added 10 % palladium-carbon (0.5 g), and the mixture is subjected to hydrogenation at 70°C under atmospheric pressure for two hours. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. To the residue is added water, and the precipitated white powder is collected by filtration to give 3-(4-methoxycarbonylphenyl)propionic acid (3.87 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 2.71 (2H, t, J=7.5Hz), 3.02 (2H, t, J=7.5Hz), 3.91 (3H, s), 7.29 (2H, d, J=8.5Hz), 7.97 (2H, d, J=8.5Hz)

Reference Example 192

To a suspension of 2-carboxybenzothiazole (6.5 g) in anhydrous dichloromethane (100 ml) are added oxalyl chloride (3.2 ml) and a drop of dimethylformamide, and the mixture is stirred at room temperature for three hours. The mixture is evaporated to remove the dichloromethane, and the residue is dissolved in acetone (100 ml), and added dropwise into an aqueous solution of sodium azide (5 g) in water (20 ml) under ice-cooling. The mixture is stirred at the same temperature for three hours, and thereto is added water. The precipitated crystals are collected by filtration, dissolved in dichloromethane (50 ml), dried, and concentrated under reduced pressure to remove the solvent. To the residue is added benzene (50 ml), and the mixture is refluxed for four hours. To the mixture is added ethyl 4-piperidinecarboxylate (5.7 g), and the mixture is refluxed for 6 hours. To the reaction solution is added water, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and concentrated under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography (solvent; dichloromethane: methanol = 200:1 $\rightarrow$ 100:1) to give 2-(4-ethoxycarbonyl-1-piperidinyl)-carbonylaminobenzothiazole (4.0 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 1.25 (3H, t, J=7Hz), 1.65-2.05 (4H, m), 2.4-2.6 (1H, m), 2.95-3.2 (2H, m), 4.0-4.2 (2H, m), 4.14 (2H, q, J=7Hz), 7.15-7.45 (2H, m), 7.58 (1H, d, J=8Hz), 7.75 (1H, d, J=8Hz), 10.11 (1H, br)

<u>Reference Example 193</u>

To a solution of methyl 2-methoxy-4-trifluoromethanesulfonyloxy-benzoate (26.8 g), t-butyl acrylate (62.5 ml), triethylamine (25 ml) in anhydrous

dimethylformamide (100 ml) are added palladium acetate (0.4 g) and 1,3-bis(diphenylphosphino)propane (0.74 g) under argon atmosphere, and the mixture is heated with stirring at 75°C for 16 hours. The reaction solution is concentrated under reduced pressure to remove the solvent, and thereto is added water. The mixture is extracted with ethyl acetate, and the extract is washed with water, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; ethyl acetate: n-hexane = 1:5) to give t-butyl 3-methoxy-4-methoxycarbonylcinnamate (23.5 g).

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 1.54 (9H, s), 3.90 (3H, s), 3.94 (3H, s), 6.42 (1H, d, J=16Hz), 7.07 (1H, d, J=1.5Hz), 7.13 (1H, dd, J=1.5, 8Hz), 7.55 (1H, d, J=16Hz), 7.80 (1H, d, J=8Hz)

Reference Example 194

To a solution of t-butyl 3-methoxy-4-methoxycarbonylcinnamate (23.5 g) in anhydrous dichloromethane (100 ml) is added trifluoroacetic acid (50 ml) under ice-cooling, and the mixture is stirred at room temperature overnight. The reaction solution is concentrated under reduced pressure to remove the solvent, and the residue is crystallized from ethanol to give 3-methoxy-4-methoxy-carbonylcinnamic acid (8.35 g).

White powder

^{1}H-NMR ($CDCl_3$+DMSO-d_6) δppm: 3.88 (3H, s), 3.94 (3H, s), 6.50 (1H, d, J=16Hz), 7.13 (1H, s), 7.15 (1H, d, J=8Hz), 7.62 (1H, d, J=16Hz), 7.78 (1H, d, J=8Hz)

Reference Example 195

To a suspension of 3-methoxy-4-methoxycarbonylcinnamic acid (8.35 g) in acetic acid (200 ml) is added 10 % palladium-carbon (1.0 g), and the mixture is subjected to hydrogenation at room temperature. The catalyst is removed by filtration, and the filtrate is concentrated under reduced pressure. The residue is crystallized from diethyl ether-n-hexane to give 3-(3-methoxy-4-methoxycarbonylphenyl)propionic acid (7.5 g).

White powder

^{1}H-NMR ($CDCl_3$) δppm: 2.70 (2H, t, J=7.5Hz), 2.98 (2H, t, J=7.5Hz), 3.88 (3H, s), 3.89 (3H, s), 5.71 (1H, br), 6.75-6.9 (2H, m), 7.75 (1H, d, J=8Hz)

Reference Example 196

To a solution of dimethyl methylphosphonate (7.7 ml) in anhydrous tetrahydrofuran (100 ml) is added dropwise a 1.66M solution of n-butyl lithium in n-hexane (43 ml) at –50°C to –60°C. Subsequently, a solution of 2-[2-(3-methoxy-4-methoxycarbonylphenyl)ethyl]carbonylaminobenzothiazole (8.72 g) in anhydrous tetrahydrofuran (50 ml) is added dropwise to the reaction solution. A yellow gummy material generates in the reaction mixture, and thereto is further added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (10 ml), and the mixture is stirred at the same temperature for two hours. To the reaction mixture is added a saturated aqueous ammonium chloride solution, and the mixture is acidified with diluted hydrochloric acid. The mixture is extracted with ethyl acetate, and the extract is washed with water, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; dichloromethane:methanol = 100:1 → 10:1) to give dimethyl [{3-methoxy-4-[2-(2-benzo-

thiazolyl)aminocarbonyl)ethyl]benzoyl}methyl]phosphonate (6.4 g), whereby the starting compound (3.1 g) is also recovered.

Yellow powder

^{1}H-NMR ($CDCl_3$) δppm: 2.80 (2H, t, J=7.5Hz), 3.05 (2H, t, J=7.5Hz), 3.73 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 3.82 (2H, d, J=21.5Hz), 6.65-6.8 (2H, m), 7.25-7.45 (2H, m), 7.60 (1H, d, J=8.5Hz), 7.64 (1H, d, J=7.5Hz), 7.82 (1H, dd, J=1Hz, J=7.5Hz), 11.49 (1H, br)

Reference Example 197

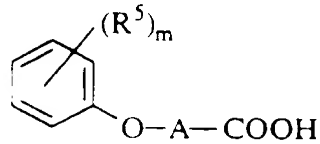
Dimethyl methylphosphonate (3.9 ml), 1.65M n-butyl lithium (22 ml) and 2-(4-ethoxycarbonyl-1-piperidinyl)carbonylaminobenzothiazole (4.0 g) are treated in the same manner as in Reference Example 196 to give dimethyl [1-(2-benzothiazolyl)aminocarbonyl)-4-piperidinylcarbonylmethyl]phosphonate (2.5 g).

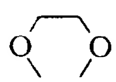
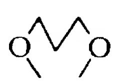
Pale yellow oil

^{1}H-NMR ($CDCl_3$) δppm: 1.5-2.05 (4H, m), 2.75-3.1 (3H, m), 3.16 (2H, d, J=28Hz), 3.76 (3H, s), 3.82 (3H, s), 4.1-4.35 (2H, m), 7.15-7.45 (2H, m), 7.57 (1H, d, J=7.5Hz), 7.74 (1H, d, J=8Hz), 10.04 (1H, br)

Using the suitable starting compounds, the compounds as listed in Table 36-1 are obtained in the same manner as in Reference Example 1.

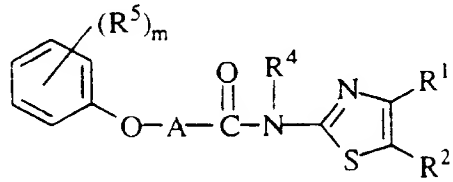
Table 36-1



Ref. Ex. No.	R^5 (substitution position)	m	A	M.p. (°C) or NMR (Salt)	Crystalline form (Solvent for recrystallization)
198	$-(CH_2)_3CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	NMR (11) (Free)	White powder
199	$-CH_2CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	111.8-112.5 (Free)	White powder (Ethyl acetate)
200	$-CH_3$ (2) $-OCH_3$ (3)	2	$-CH_2-$	NMR (17) (Free)	Yellow powder
201	$-(CH_2)_3CH_3$ (2) $-OCH_3$ (3)	2	$-CH_2-$	NMR (18) (Free)	White powder
202	$-OCH_3$ (3)	1	$-\overset{CH_3}{\overset{\vert}{C}H}-$	93-95 (Free)	White powder (Diethyl ether-n-hexane)
203	 (2,3)	2	$-CH_2-$	152-154 (Free)	Colorless needles
204	 (2,3)	2	$-CH_2-$	122-123 (Free)	White powder
205	$-(CH_2)_2CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	95-98 (Free)	White powder
206	$-CH(CH_3)_2$ (2) $-OCH_3$ (5)	2	$-CH_2-$	NMR (50) (Free)	White powder
207	$-(CH_2)_5CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	NMR (51) (Free)	White powder
208	$-CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	NMR (55) (Free)	White powder
209	$-OCH_3$ (2, 5)	2	$-CH_2-$	NMR (60) (Free)	White powder
210	$-OC_2CH_5$ (2) $-OCH_3$ (5)	2	$-CH_2-$	NMR (62) (Free)	White powder

Using the suitable starting compounds, the compounds as listed in Tables 36-2 to 36-9 are obtained in the same manner as Reference Example 2.

Table 36-2



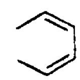
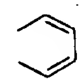
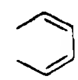
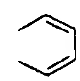
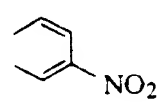
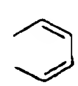
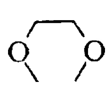
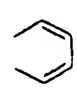
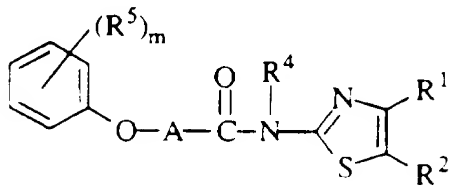
Ref. Ex. No.	R^5 (substitution position)	m	A	R^4	R^1 and R^2	M.p. (°C) or NMR (salt)	Crystalline form (solvent for recrystal.)
211	$-(CH_2)_3CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		130.0-130.3 (Free)	Yellow powder (Ethyl acetate-n-hexane)
212	$-CH_2CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		193-196 (Free)	Pale yellow needles (Ethyl acetate-n-hexane)
213	$-(CH_2)_3CH_3$ (2) $-OCH_3$ (3)	2	$-CH_2-$	H		NMR (19) (Free)	Yellow powder
214	$-CH_3$ (2) $-OCH_3$ (3)	2	$-CH_2-$	H		NMR (39) (Free)	Yellow powder
215	$-OCH_3$ (3)	1	$-CH_2-$	H		190-191 (Free)	Pale yellow powder
216	$-OCH_3$ (3)	1	$-\underset{}{CH}(CH_3)-$	H		NMR (42) (Free)	Orange oil
217	 (2,3)	2	$-CH_2-$	H		148-149 (Free)	Pale yellow powder (Ethanol-n-hexane)

Table 36-3



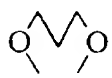
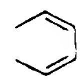
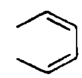
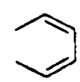
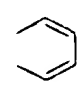
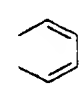
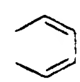
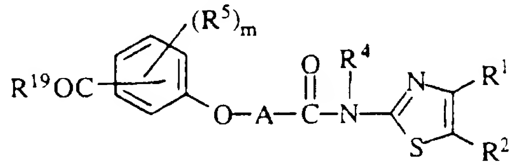
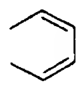
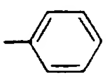
Ref. Ex. No.	R^5 (substitution position)	m	A	R^4	R^1 and R^2	M.p (°C) or NMR (salt)	Crystalline form (solvent for recrystal.)
218	 (2,3)	2	$-CH_2-$	H		126-128 (Free)	Pale yellow powder (Ethanol-n-hexane)
219	$-(CH_2)_2CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		140-142 (Free)	Pale orange powder (Ethanol)
220	$-CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		NMR (52) (Free)	Yellow powder
221	$-CH(CH_3)_2$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		NMR (53)	Pale red powder
222	$-(CH_2)_5CH_3$ (2) $-OCH_3$ (5)	2	$-CH_2-$	H		NMR (54)	White powder
223	$-OCH_3$ (2 & 5)	2	$-CH_2-$	H		NMR (61) (Free)	Pale brown powder

Table 36-4



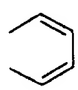
Reference Example 224

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5: $-OCH_2-$ (3-position)

M.p. 197.0-197.5°C Crystalline form: Yellow powder
Solvent for recrystallization: Ethyl acetate-dimethylformamide Form: Free

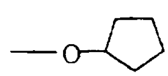
Reference Example 225

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5: $-OCH_2CH=CH_2$ (3-position)
M.p. 130-132°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

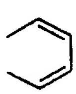
Reference Example 226

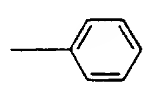
R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5:  (3-position)

M.p. 131.5-132.5°C Crystalline form: White powder
Solvent for recrystallization: n-Hexane-ethyl acetate-dichloromethane
Form: Free

Reference Example 227

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5:  (3-position)

M.p. 169.9-170.3°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Table 36-5

Reference Example 228

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 2

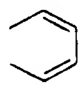
R^{19}: $-OCH_3$ (4-position)

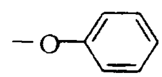
R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (3-position)

M.p. 147.0-147.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Reference Example 229

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5:  (3-position)

M.p. 142.0-143.0°C Crystalline form: White powder

Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Reference Example 230

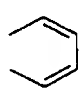
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5: $-SCH_3$ (3-position)

NMR (22) Crystalline form: Pale yellow powder

Form: Free

Reference Example 231

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 2

R^{19}: $-OCH_3$ (4-position)

R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (3-position)

NMR (27) Crystalline form: Pale yellow powder

Form: Free

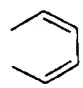
Table 36-6

Reference Example 232

R^1
R^2 :  R^4: H A: $-CH_2-$ m: 2

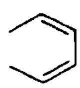
R^{19}: $-OCH_3$ (4-position)
R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)
NMR (35) Crystalline form: Orange powder
Form: Free

Reference Example 233

R^1
R^2 :  R^4: H A: $-CH_2-$ m: 2

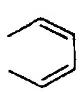
R^{19}: $-OCH_3$ (4-position)
R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (3-position)
NMR (36) Crystalline form: Orange powder

Reference Example 234

R^1
R^2 :  R^4: H A: $-(CH_2)_3-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5: $-OCH_3$ (3-position)
M.p. 186-188°C Crystalline form: White powder
Form: Free

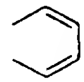
Reference Example 235

R^1
R^2 :  R^4: H A: $-CH_2-$ m: 2

R^{19}: $-OCH_3$ (4-position)
R^5: $-CH_2CH=CH_2$ (2-position) & $-OCH_3$ (5-position)
M.p. 187-189°C Crystalline form: Pale yellow powder
Form: Free

Table 36-7

Reference Example 236

R^1 :  R^4: H A: $-CH_2-$ m: 2

R^2

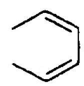
R^{19}: $-OCH_3$ (4-position)

R^5: $-OCH_3$ (2-position) & $-N(CH_3)_2$ (3-position)

NMR (46) Crystalline form: White powder

Form: Free

Reference Example 237

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

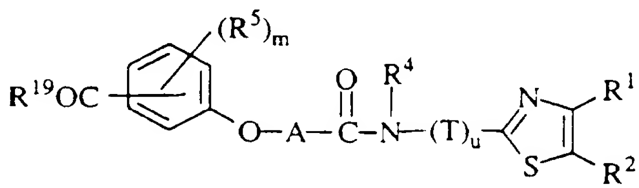
R^{19}: $-OCH_3$ (4-position)

R^5: $-N(CH_3)_2$ (2-position)

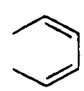
NMR (65) Crystalline form: White powder

Form: Free

Table 36-8



Reference Example 238

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

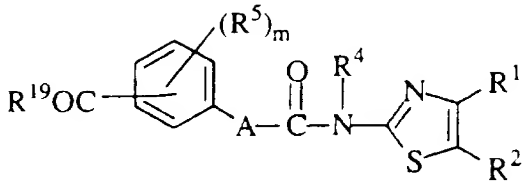
R^{19}: $-OCH_3$ (4-position) R^5: $-OCH_3$ (3-position)

T: $-CH_2-$ u: 1

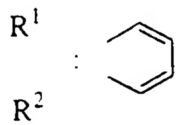
NMR (48) Crystalline form: White powder

Form: Free

Table 36-9



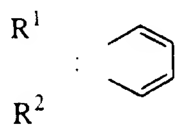
Reference Example 239



R^{4}: H A: $-(CH_2)_2-$ m: 1

R^{19}: $-OCH_3$ (4-position) R^5: H
NMR (73) Crystalline form: Yellow powder
Form: Free

Reference Example 240

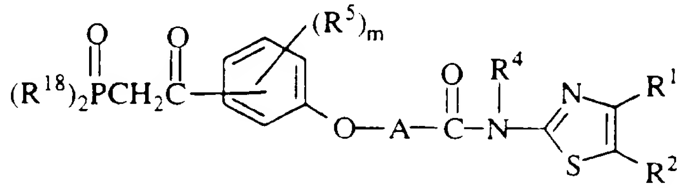


R^{4}: H A: $-(CH_2)_2-$ m: 1

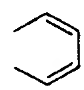
R^{19}: $-OCH_3$ (4-position)
R^5: $-OCH_3$ (3-position)
NMR (75) Crystalline form: Yellow powder
Form: Free

Using the suitable starting compounds, the compounds as listed in Table 36-10 to 36-16 are obtained in the same manner as in Reference Example 3.

Table 36-10



Reference Example 241

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

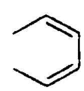
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-OCH_2CH=CH_2$ (3-position)

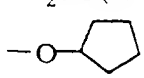
M.p. 134-135°C Crystalline form: White powder

Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Reference Example 242

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

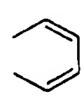
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5:  (3-position)

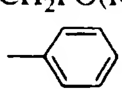
NMR (8) Crystalline form: Yellow oil

Form: Free

Reference Example 243

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

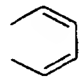
R^5:  (3-position)

NMR (10) Crystalline form: Yellow oil

Form: Free

Table 36-11

Reference Example 244

R^1 :  R^4: H A: $-CH_2-$ m: 2

R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (3-position)

M.p. 156.5-157.4 °C Crystalline form: White needles

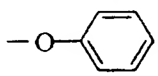
Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Reference Example 245

R^1 :  R^4: H A: $-CH_2-$ m: 1

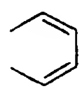
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5:  (3-position)

NMR (16) Crystalline form: Yellow amorphous Form: Free

Reference Example 246

R^1 :  R^4: H A: $-CH_2-$ m: 1

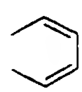
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-SCH_3$ (3-position)

NMR (23) Crystalline form: Pale brown powder Form: Free

Reference Example 247

R^1 :  R^4: H A: $-CH_2-$ m: 2

R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (3-position)

NMR (28) Crystalline form: White powder Form: Free

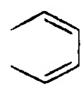
Table 36-12

Reference Example 248

R^1 :  R^4: H A: $-CH_2-$ m: 2
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)
NMR (37) Crystalline form: Pale red powder Form: Free

Reference Example 249

R^1 :  R^4: H A: $-CH_2-$ m: 2
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (3-position)
NMR (38) Crystalline form: Pale red powder Form: Free

Reference Example 250

R^1 :  R^4: H A: $-(CH_2)_3-$ m: 1
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-OCH_3$ (3-position)
M.p. 140-142°C Crystalline form: Colorless prisms
Solvent for recrystallization: Ethanol Form: Free

Reference Example 251

R^1 :  R^4: H A: $-CH_2-$ m: 2
R^2

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-CH_2CH=CH_2$ (2-position) & $-OCH_3$ (5-position)
M.p. 125-128°C Crystalline form: Pale brown prisms
Solvent for recrystallization: Ethanol-n-hexane Form: Free

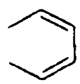
Table 36-13

Reference Example 252

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 2

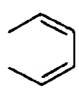
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-OCH_3$ (2-position) & $-N(CH_3)_2$ (3-position)
NMR (47) Crystalline form: Pale yellow powder Form: Free

Reference Example 253

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 2

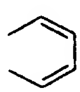
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-Br$ (2-position) & $-OCH_3$ (5-position)
M.p. 196-199°C Crystalline form: White powder
Solvent for recrystallization: Ethanol Form: Free

Reference Example 254

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

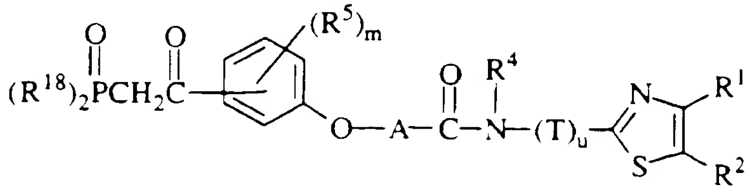
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-N(CH_3)_2$ (2-position)
NMR (66) Crystalline form: Yellow oil Form: Free

Reference Example 254A

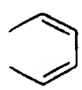
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)
R^5: $-OCH_3$ (2-position)
NMR (77) Crystalline form: White powder Form: Free

Table 36-14



Reference Example 255

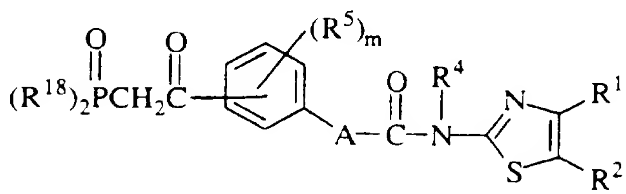
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-OCH_3$ (3-position) T: $-CH_2-$ u: 1

NMR (49) Crystalline form: Brown oil Form: Free

Table 36-15



Reference Example 256

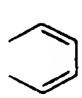
R^1 :  R^2 R^4: H A: $-(CH_2)_2-$ m: 1

$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: H

NMR (74) Crystalline form: Pale brown oil Form: Free

Reference Example 257

R^1 :  R^2 R^4: H A: $-(CH_2)_2-$ m: 1

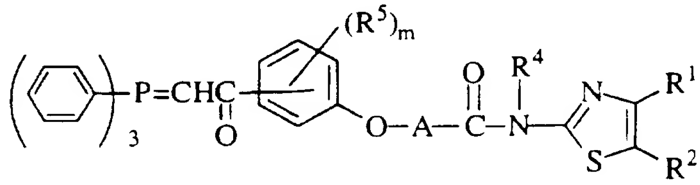
$-COCH_2PO(R^{18})_2$: $-COCH_2PO(OCH_3)_2$ (4-position)

R^5: $-OCH_3$ (3-position)

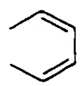
NMR (76) Crystalline form: Yellow powder Form: Free

Using the suitable starting compounds, the compounds as listed in Table 36-16 are obtained in the same manner as in Reference Example 5 or 6.

Table 36-16



Reference Example 258

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 2

R^5: $-OCH_3$ (2 & 3-positions)

NMR (67) Crystalline form: Pale yellow amorphous Form: Free

Reference Example 259

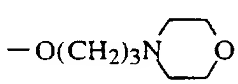
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^5: $-O(CH_2)_3Cl$ (3-position)

NMR (68) Crystalline form: Colorless amorphous Form: Free

Reference Example 260

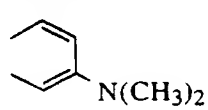
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^5: 

(3-position)

NMR (69) Crystalline form: Pale yellow amorphous Form: Free

Reference Example 261

R^1 : 

R^2 R^4: H A: $-CH_2-$ m: 1

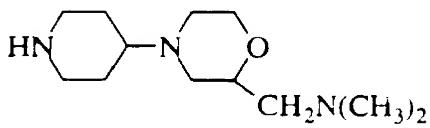
R^5: $-OCH_3$ (3-position)

NMR (70) Crystalline form: Dark brown amorphous Form: Free

Using the suitable starting compounds, the compounds as listed in Table 36-17 are obtained in the same manner as in Reference Example 7, 8 or 9.

Table 36-17

Reference Example 262

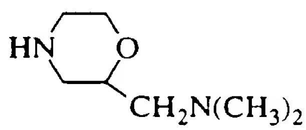


Colorless oil

Form: Free

NMR (71)

Reference Example 263



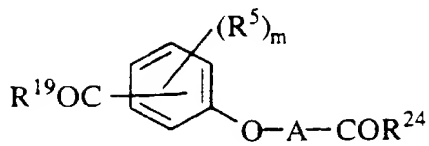
Pale yellow oil

Form: Free

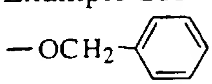
NMR (72)

Using the suitable starting compounds, the compounds as listed in Tables 36-18 to 36-21 are obtained in the same manner as in Reference Example 187.

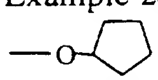
Table 36-18

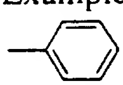


Reference Example 264
R^5: –OH (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (1) Crystalline form: White solid Form: Free

Reference Example 265
R^5:  (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (2) Crystalline form: White solid Form: Free

Reference Example 266
R^5: $-OCH_2CH=CH_2$ (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (4) Crystalline form: Colorless oil Form: Free

Reference Example 267
R^5:  (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (6) Crystalline form: Yellow oil Form: Free

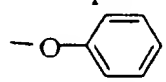
Reference Example 268
R^5:  (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (9) Crystalline form: Colorless oil Form: Free

Reference Example 269
R^5: $-CH_2CH=CH_2$ (2-position) & –OH (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
M.p. 93.1-93.8°C Crystalline form: Colorless needles
Solvent for recrystallization: n-Hexane-ethyl acetate Form: Free

Reference Example 270
R^5: $-(CH_2)_2CH_3$ (2-position) & –OH (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (12) Crystalline form: White solid Form: Free

Table 36-19

Reference Example 271
R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (13) Crystalline form: Colorless oil Form: Free

Reference Example 272
R^5:  (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (15) Crystalline form: Colorless oil Form: Free

Reference Example 273
R^5: $-SCH_3$ (3-position) A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (20) Crystalline form: Pale yellow powder Form: Free

Reference Example 274
R^5: $-(CH_2)_3CH_3$ (2-position) & $-OH$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (24) Crystalline form: Pale brown powder Form: Free

Reference Example 275
R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (25) Crystalline form: White powder Form: Free

Reference Example 276
R^5: $-CH_2CH_3$ (2-position) & $-OH$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (29) Crystalline form: White powder Form: Free

Reference Example 277
R^5: $-CH_3$ (2-position) & $-OH$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (30) Crystalline form: White powder Form: Free

Table 36-20

Reference Example 278
R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (31) Crystalline form: Colorless needles Form: Free

Reference Example 279
R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (32) Crystalline form: Colorless oil Form: Free

Reference Example 280
R^5:$-OH$ (3-position)
A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OC_2H_5$
NMR (40) Crystalline form: Colorless oil Form: Free

Reference Example 281
R^5:$-OCH_3$ (3-position)
A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OC_2H_5$
NMR (41) Crystalline form: Pale brown powder Form: Free

Reference Example 282
R^5:$-OCH_3$ (3-position)
A: $-(CH_2)_3-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
M.p. 48-50°C Crystalline form: White powder
Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Reference Example 283
R^5: $-OCH_3$ (2-position) & $-NH_2$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (44) Crystalline form: Yellow oil Form: Free

Reference Example 284
R^5: $-OCH_3$ (2-position) & $-N(CH_3)_2$ (3-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (45) Crystalline form: Brown oil Form: Free

Table 36-21

Reference Example 285

R^5: $-Br$ (2-position) & $-OH$ (5-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (56) Crystalline form: White powder Form: Free

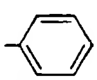
Reference Example 286

R^5: $-Br$ (2-position) & $-OCH_3$ (5-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_3$
NMR (57) Crystalline form: White powder Form: Free

Reference Example 287

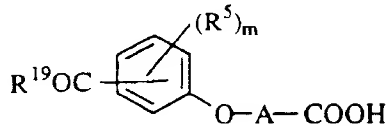
R^5: $-NH_2$ (2-position) & $-OCH_3$ (5-position)
A: $-CH_2-$ m: 2
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OC_2H_5$
NMR (59) Crystalline form: White powder Form: Free

Reference Example 288

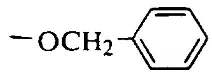
R^5: $-N(CH_3)_2$ (2-position)
A: $-CH_2-$ m: 1
$-COR^{19}$: $-COOCH_3$ (4-position) R^{24}: $-OCH_2-$ 
NMR (63) Crystalline form: Yellow oil Form: Free

Using the suitable starting compounds, the compounds as listed in Tables 36-22 to 36-23 are obtained in the same manner as in Reference Example 1 or 194.

Table 36-22



Reference Example 289

R^5:  (3-position)

A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)

NMR (3) Crystalline form: White solid Form: Free

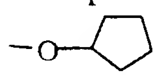
Reference Example 290

R^5: $-OCH_2CH{=}CH_2$ (3-position)

A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)

NMR (5) Crystalline form: White solid Form: Free

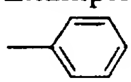
Reference Example 291

R^5:  (3-position)

A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)

NMR (7) Crystalline form: Pale yellow oil Form: Free

Reference Example 292

R^5:  (3-position)

A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)

M.p. 124.5-126.0°C Crystalline form: White powder

Solvent for recrystallization: Ethyl acetate Form: Free

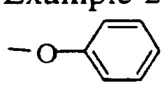
Reference Example 293

R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)

NMR (14) Crystalline form: White solid Form: Free

Reference Example 294

R^5:  (3-position)

A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)

M.p. 131.5-132.0°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethyl acetate Form: Free

Reference Example 295

R^5: $-SCH_3$ (3-position) A: $-CH_2-$ m: 1

$-COR^{19}$: $-COOCH_3$ (4-position) NMR (21)

Crystalline form: White powder Form: Free

Table 36-23

Reference Example 296
R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (26) Crystalline form: White powder Form: Free

Reference Example 297
R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (33) Crystalline form: White powder

Reference Example 298
R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (3-position)
A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (34) Crystalline form: White powder

Reference Example 299
R^5: $-OCH_3$ (3-position)
A: $-(CH_2)_3-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)
M.p. 89-90°C Crystalline form: Colorless needles
Solvent for recrystallization: Water-ethanol Form: Free

Reference Example 300
R^5: $-CH_2CH{=}CH_2$ (2-position) & $-OCH_3$ (5-position)
A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (43) Crystalline form: White powder Form: Free

Reference Example 301
R^5: $-Br$ (2-position) & $-OCH_3$ (5-position)
A: $-CH_2-$ m: 2 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (58) Crystalline form: White powder Form: Free

Reference Example 302
R^5: $-N(CH_3)_2$ (2-position)
A: $-CH_2-$ m: 1 $-COR^{19}$: $-COOCH_3$ (4-position)
NMR (64) Crystalline form: White amorphous Form: Free

<u>Reference Example 303</u>

Using the suitable starting compounds, the following compounds are obtained in the same manner as in Reference Example 6.

Methyl α-(2,3-dihydroxy-4-acetylphenoxy)acetate:

White powder

^{1}H-NMR (DMSO-d_6) δppm: 2.56 (3H, s), 3.69 (3H, s), 4.91 (2H, s), 6.49 (1H, d, J=9.1Hz), 7.35 (1H, d, J=9.1Hz), 8.79 (1H, s), 12.31 (1H, s)

Methyl α-(2,3-dimethoxy-4-acetylphenoxy)acetate:

White solid

^{1}H-NMR ($CDCl_3$) δppm: 2.60 (3H, s), 3.81 (3H, s), 3.93 (3H, s), 3.99 (3H, s), 4.75 (2H, s), 6.57 (1H, d, J=8.9Hz), 7.48 (1H, d, J=8.9Hz)

Methyl α-[2,3-dimethoxy-4-(2-bromoacetyl)phenoxy]acetate:

Colorless oil

^{1}H-NMR ($CDCl_3$) δppm: 3.81 (3H, s), 3.93 (3H, s), 4.07 (3H, s), 4.57 (2H, s), 4.76 (2H, s), 6.58 (1H, d, J=8.9Hz), 7.54 (1H, d, J=8.9Hz)

(2,3-Dimethoxy-4-methoxycarbonylmethoxybenzoyl)methylenetriphenyl-phosphorane:

Colorless amorphous

^{1}H-NMR ($CDCl_3$) δppm: 3.77 (3H, s), 3.94 (6H, s), 4.61 (1H, brd, J=27.8Hz), 4.70 (2H, s), 6.56 (1H, d, J=8.8Hz), 7.38-7.80 (16H, m)

Ethyl α-[3-(3-chloropropoxy)-4-acetylphenoxy)acetate:

Yellow oil

^{1}H-NMR ($CDCl_3$) δppm: 1.31 (3H, t, J=7Hz), 2.2-2.5 (2H, m), 2.57 (3H, s), 3.77 (2H, t, J=6.5Hz). 4.30 (2H, t, J=7Hz), 4.66 (2H, s), 6.47 (1H, dd, J=2H, J=8.5Hz), 6.57 (1H, d, J=2Hz), 7.81 (1H, d, J=8.5Hz)

Ethyl α-[3-(3-chloropropoxy)-4-(2-bromoacetyl)phenoxy]acetate:

Colorless oil

^{1}H-NMR ($CDCl_3$) δppm: 1.31 (3H, t, J=7Hz), 2.25-2.55 (2H, m), 3.55-3.85

(2H, m), 4.15-4.4 (4H, m), 4.50 (2H, s), 4.68 (2H, s), 6.51 (1H, dd, J=2Hz, J=9Hz), 6.59 (1H, d, J=2Hz), 7.89 (1H, d, J=9Hz)

[2-(3-Chloropropoxy)-4-ethoxycarbonylmethoxybenzoyl]methylenetriphenylphosphorane:

Pale brown amorphous

^{1}H-NMR ($CDCl_3$) δppm: 1.31 (3H, t, J=7Hz), 2.2-2.7 (2H, m), 3.67 (2H, d, J=5.5Hz), 4.27 (2H, q, J=7Hz), 4.2-4.4 (2H, m), 4.66 (2H, s), 6.20 (1H, br), 6.47 (1H, dd, J=2Hz, J=9Hz), 6.57 (1H, d, J=2Hz), 7.4-8.0 (16H, m)

(2,3-Dimethoxy-4-carboxymethoxybenzoyl)methyltriphenylphosphonium chloride:

Colorless prisms (recrystallized from diluted hydrochloric acid)

M.p. 137-151°C (decomposed)

^{1}H-NMR (DMSO-d_6) δppm: 3.78 (3H, s), 3.81 (3H, s), 4.69 (2H, s), 6.63 (1H, d, J=8.9Hz), 7.28 (1H, d, J=8.9Hz), 7.50-7.80 (15H, m)

[2-(3-Chloropropoxy)-4-carboxymethoxybenzoyl]methyltriphenylphosphonium chloride:

Pale yellow amorphous

^{1}H-NMR ($CDCl_3$) δppm: 2.1-2.45 (2H, m), 3.63 (2H, t, J=6.5Hz), 4.04 (2H, t, J=5Hz), 4.49 (2H, s), 6.35 (1H, dd, J=2Hz, J=7Hz), 6.48 (1H, d, J=2Hz), 7.35-7.9 (16H, m)

^{1}H-NMR spectrum (NMR (1) to NMR (77)) as described in Tables 36-1 to 36-23 are as follows:

NMR (1) ($CDCl_3$) δppm: 3.81 (3H, s), 3.91 (3H, s), 4.65 (2H, s), 6.39 (1H, d,

J=2.6Hz), 6.45 (1H, dd, J=2.6Hz, J=8.8Hz), 7.73 (1H, d, J=8.8Hz), 10.97 (1H, s)

NMR (2) ($CDCl_3$) δppm: 3.80 (3H, s), 3.87 (3H, s), 4.64 (2H, s), 5.16 (2H, s), 6.42 (1H, dd, J=2.4Hz, J=8.7Hz), 6.60 (1H, d, J=2.4Hz), 7.30-7.43 (3H, m), 7.49-7.52 (2H, m), 7.85 (1H, d, J=8.7Hz)

NMR (3) (DMSO-d_6) δppm: 3.76 (3H, s), 4.76 (2H, s), 5.19 (2H, s), 6.54 (1H, dd, J=2.3Hz, J=8.7Hz), 6.76 (1H, d, J=2.3Hz), 7.27-7.44 (3H, m), 7.49-7.53 (2H, m), 7.69 (1H, d, J=8.7Hz), 13.07 (1H, brs)

NMR (4) ($CDCl_3$) δppm: 3.82 (3H, s), 3.86 (3H, s), 4.58-4.62 (2H, m), 4.66 (2H, s), 5.28-5.58 (2H, m), 5.98-6.19 (1H, m), 6.41 (1H, dd, J=2.4Hz, J=8.7Hz), 6.54 (1H, d, J=2.4Hz), 7.83 (1H, d, J=8.7Hz)

NMR (5) (DMSO-d_6) δppm: 3.74 (3H, s), 4.59-4.63 (2H, m), 4.75 (2H, s), 5.21-5.29 (2H, m), 5.93-6.09 (1H, m), 6.52 (1H, dd, J=2.3Hz, J=8.7Hz), 6.64 (1H, d, J=2.3Hz), 7.67 (1H, d, J=8.7Hz), 13.05 (1H, brs)

NMR (6) ($CDCl_3$) δppm: 1.52-2.00 (8H, m), 3.82 (3H, s), 3.84 (3H, s), 4.66 (2H, s), 4.73-4.84 (1H, m), 6.37 (1H, dd, J=2.4Hz, J=8.7Hz), 6.53 (1H, d, J=2.4Hz), 7.79 (1H, d, J=8.7Hz)

NMR (7) ($CDCl_3$) δppm: 1.52-2.03 (8H, m), 3.84 (3H, s), 4.71 (2H, s), 4.30-5.20 (2H, m), 6.40 (1H, dd, J=2.4Hz, J=8.7Hz), 6.54 (1H, d, J=2.4Hz), 7.80 (1H, d, J=8.7Hz)

NMR (8) ($CDCl_3$) δppm: 1.65-2.12 (8H, m), 3.74 (3H, s), 3.78 (3H, s), 3.70-3.88 (2H, m), 4.79 (2H, s), 4.83-4.94 (1H, m), 6.40-6.62 (2H, m), 7.32-7.42 (1H, m), 7.44-7.52 (1H, m), 7.79-7.90 (3H, m), 8.31-10.20 (1H, brs)

NMR (9) ($CDCl_3$) δppm: 3.61 (3H, s), 3.81 (3H, s), 4.70 (2H, s), 6.83-6.97

(2H, m), 7.22-7.33 (2H, m), 7.33-7.45 (3H, m), 7.85 (1H, d, J=8.8Hz)

NMR (10) ($CDCl_3$) δppm: 3.50-3.70 (8H, m), 4.79 (2H, s), 6.77-6.97 (2H, m), 7.09-7.49 (8H, m), 7.58-7.89 (2H, m), 9.97-10.81 (1H, brs)

NMR (11) ($CDCl_3$) δppm: 0.88 (3H, t, J=7.2Hz), 1.26-1.47 (2H, m), 1.47-1.66 (2H, m), 2.56 (2H, t, J=7.5Hz), 3.78 (3H, s), 4.66 (2H, s), 6.33 (1H, d, J=2.4Hz), 6.46 (1H, dd, J=2.4Hz, J=8.3Hz), 7.05 (1H, d, J=8.3Hz)

NMR (12) ($CDCl_3$) δppm: 0.92 (3H, t, J=7.4Hz), 1.48-1.70 (2H, m), 2.65-2.78 (2H, m), 3.79 (3H, s), 3.90 (3H, s), 4.70 (2H, s), 6.25 (1H, d, J=8.9Hz), 7.65 (1H, d, J=8.9Hz), 11.08 (1H, s)

NMR (13) ($CDCl_3$) δppm: 0.94 (3H, t, J=7.3Hz), 1.49-1.71 (2H, m), 2.63-2.77 (2H, m), 3.80 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 4.70 (2H, s), 6.48 (1H, d, J=8.8Hz), 7.70 (1H, d, J=8.8Hz)

NMR (14) ($CDCl_3$) δppm: 0.93 (3H, t, J=7.3Hz), 1.47-1.70 (2H, m), 2.62-2.76 (2H, m), 3.83 (3H, s), 3.90 (3H, s), 4.74 (2H, s), 6.51 (1H, d, J=8.8Hz), 7.20 (1H, brs), 7.72 (1H, d, J=8.8Hz)

NMR (15) ($CDCl_3$) δppm: 3.77 (3H, s), 3.79 (3H, s), 4.59 (2H, s), 6.45 (1H, d, J=2.5Hz), 6.65 (1H, dd, J=2.5Hz, J=8.8Hz), 6.92-7.03 (2H, m), 7.03-7.17 (1H, m), 7.26-7.40 (2H, m), 7.91 (1H, d, J=8.8Hz)

NMR (16) ($CDCl_3$) δppm: 3.72 (3H, s), 3.77 (3H, s), 3.81 (2H, d, J=21.6Hz), 4.68 (2H, s), 6.34 (1H, d, J=2.4Hz), 6.62 (1H, dd, J=2.4Hz, J=8.8Hz), 7.04-7.15 (2H, m), 7.15-7.47 (5H, [illegible]), 7.68-7.83 (2H, m), 7.86 (1H, d, J=8.8Hz), 10.65 (1H, brs)

NMR (17) (DMSO-d_6) δppm: 2.02 (3H, s), 3.75 (3H, s), 4.64 (2H, s), 6.47 (1H, d, J=8.3Hz), 6.60 (1H, d, J=8.3Hz), 7.07 (1H, t, J=8.3Hz), 12.93 (1H, brs)

NMR (18) (DMSO-d_6) δppm: 0.86 (3H, t, J=7.2Hz), 1.13-1.51 (4H, m), 2.59 (2H, t, J=7.6Hz), 3.74 (3H, s), 4.63 (2H, s), 6.46 (1H, d, J=8.3Hz), 6.59 (1H, d, J=8.3Hz), 7.06 (1H, t, J=8.3Hz), 12.89 (1H, brs)

NMR (19) ($CDCl_3$) δppm: 0.97 (3H, t, J=7.1Hz), 1.31-1.68 (4H, m), 2.77 (2H, t, J=7.0Hz), 3.84 (3H, s), 4.75 (2H, s), 6.51 (1H, d, J=8.2Hz), 6.64 (1H, d, J=8.2Hz), 7.14 (1H, t, J=8.2Hz), 7.26-7.39 (1H, m), 7.39-7.52 (1H, m), 7.73-7.90 (2H, m), 9.70 (1H, brs)

NMR (20) ($CDCl_3$) δppm: 2.43 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 4.70 (2H, s), 6.59 (1H, dd, J=8.8Hz, J=2.4Hz), 6.81 (1H, d, J=2.4Hz), 8.00 (1H, d, J=8.8Hz)

NMR (21) (DMSO-d_6) δppm: 2.39 (3H, s), 3.77 (3H, s), 4.81 (2H, s), 6.62-6.83 (2H, m), 7.89 (1H, d, J=9.1Hz), 13.14 (1H, brs)

NMR (22) ($CDCl_3$) δppm: 2.48 (3H, s), 3.90 (3H, s), 4.82 (2H, s), 6.69 (1H, dd, J=8.7Hz, J=2.4Hz), 6.86 (1H, d, J=2.4Hz), 7.36 (1H, dt, J=1.2Hz, J=7.7Hz), 7.48 (1H, dt, J=1.2Hz, J=7.7Hz), 7.84 (2H, t, J=7.7Hz), 8.05 (1H, d, J=8.7Hz), 9.91 (1H, brs)

NMR (23) ($CDCl_3$) δppm: 2.41 (3H, s), 3.63 (2H, d, J=22.6Hz), 3.80 (6H, d, J=11.2Hz), 4.82 (2H, s), 6.71 (1H, dd, J=8.8Hz, J=2.4Hz), 6.85 (1H, d, J=2.4Hz), 7.34 (1H, dt, J=1.3Hz, J=9.2Hz), 7.47 (1H, dt, J=1.3H, J=9.2Hz), 7.82 (2H, t, J=9.2Hz), 8.01 (1H, d, J=8.8Hz)

NMR (24) ($CDCl_3$) δppm: 0.93 (3H, t, J=7.0Hz), 1.19-1.62 (4H, m), 2.73 (2H, t, J=7.0Hz), 3.79 (3H, s), 3.91 (3H, s), 4.70 (2H, s), 6.27 (1H, d, J=9.0Hz), 7.67 (1H, d, J=9.0Hz), 11.07 (1H, s)

NMR (25) ($CDCl_3$) δppm: 0.94 (3H, t, J=7.2Hz), 1.29-1.63 (4H, m), 2.72

(2H, t, J=7.1Hz), 3.80 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 4.70 (2H, s), 6.50 (1H, d, J=8.8Hz), 7.72 (1H, d, J=8.8Hz)

NMR (26) (DMSO-d_6) δppm: 0.88 (3H, t, J=7.1Hz), 1.19-1.61 (4H, m), 2.60 (2H, t, J=6.7Hz), 3.70 (3H, s), 3.78 (3H, s), 4.77 (2H, s), 6.71 (1H, d, J=8.8Hz), 7.60 (1H, d, J=8.8Hz), 13.05 (1H, brs)

NMR (27) ($CDCl_3$) δppm: 0.99 (3H, t, J=7.1Hz), 1.37-1.71 (4H, m), 2.80 (2H, t, J=6.9Hz), 3.87 (3H, s), 3.91 (3H, s), 4.82 (2H, s), 6.66 (1H, d, J=8.8Hz), 7.34 (1H, dt, J=1.3Hz, J=7.7Hz), 7.46 (1H, dt, J=1.3Hz, J=7.7Hz), 7.69-7.90 (3H, m), 9.62 (1H, brs)

NMR (28) ($CDCl_3$) δppm: 1.00 (3H, t, J=7.0Hz), 1.39-1.73 (4H, m), 2.78 (2H, t, J=8.0Hz), 3.76 (6H, d, J=11.4Hz), 3.79 (3H, s), 3.81 (2H, d, J=22.1Hz), 4.82 (2H, s), 6.69 (1H, d, J=8.8Hz), 7.34 (1H, t, J=8.6Hz), 7.46 (1H, t, J=8.6Hz), 7.57 (1H, d, J=8.8Hz), 7.82 (2H, t, J=8.6Hz), 9.87 (1H, brs)

NMR (29) ($CDCl_3$) δppm: 1.14 (3H, t, J=7.5Hz), 2.75 (2H, q, J=7.5Hz), 3.80 (3H, s), 3.91 (3H, s), 4.71 (2H, s), 6.28 (1H, d, J=9.0Hz), 7.67 (1H, d, J=9.0Hz), 11.08 (1H, s)

NMR (30) ($CDCl_3$) δppm: 2.18 (3H, s), 3.80 (3H, s), 3.91 (3H, s), 4.71 (2H, s), 6.28 (1H, d, J=9.0Hz), 7.67 (1H, d, J=9.0Hz), 11.11 (1H, s)

NMR (31) ($CDCl_3$) δppm: 2.34 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.89 (3H, s), 4.70 (2H, s), 6.51 (1H, d, J=8.8Hz), 7.71 (1H, d, J=8.8Hz)

NMR (32) ($CDCl_3$) δppm: 1.18 (3H, t, J=7.5Hz), 2.76 (2H, q, J=7.5Hz), 3.80 (3H, s), 3.84 (3H, s), 3.89 (3H, s), 4.71 (2H, s), 6.51 (1H, d, J=8.8Hz), 7.73 (1H, d, J=8.8Hz)

NMR (33) (DMSO-d_6) δppm: 2.10 (3H, s), 3.70 (3H, s), 3.78 (3H, s), 4.78

(2H, s), 6.72 (1H, d, J=8.9Hz), 7.59 (1H, d, J=8.9Hz), 13.11 (1H, brs)

NMR (34) (DMSO-d_6) δppm: 1.08 (3H, t, J=7.4Hz), 2.62 (2H, q, J=7.4Hz), 3.72 (3H, s), 3.78 (3H, s), 4.79 (2H, s), 6.72 (1H, d, J=8.9Hz), 7.60 (1H, d, J=8.9Hz), 13.09 (1H, brs)

NMR (35) ($CDCl_3$) δppm: 2.31 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 4.82 (2H, s), 6.65 (1H, d, J=8.8Hz), 7.34 (1H, dt, J=1.2Hz, J=7.6Hz), 7.46 (1H, dt, J=1.2Hz, J=7.6Hz), 7.69-7.89 (3H, m), 9.79 (1H, brs)

NMR (36) ($CDCl_3$) δppm: 1.27 (3H, t, J=7.6Hz), 2.83 (2H, q, J=7.6Hz), 3.87 (3H, s), 3.91 (3H, s), 4.83 (2H, s), 6.66 (1H, d, J=8.8Hz), 7.30 (1H, dt, J=1.3Hz, J=7.3Hz), 7.46 (1H, dt, J=1.3Hz, J=7.3Hz), 7.70-7.90 (3H, m), 9.72 (1H, brs)

NMR (37) ($CDCl_3$) δppm: 2.33 (3H, s), 3.77 (6H, d, J=11.1Hz), 3.80 (3H, s), 3.81 (2H, d, J=22.0Hz), 4.82 (2H, s), 6.69 (1H, d, J=8.8Hz), 7.35 (1H, dt, J=1.3Hz, J=7.9Hz), 7.47 (1H, dt, J=1.3Hz, J=7.9Hz), 7.61 (1H, d, J=8.8Hz), 7.82 (2H, t, J=7.9Hz), 9.87 (1H, brs)

NMR (38) ($CDCl_3$) δppm: 1.29 (3H, t, J=7.5Hz), 2.83 (2H, q, J=7.5Hz), 3.76 (6H, d, J=11.2Hz), 3.80 (2H, d, J=22.1Hz), 3.81 (3H, s), 4.83 (2H, s), 6.70 (1H, d, J=8.8Hz), 7.38 (1H, dt, J=1.4Hz, J=8.6Hz), 7.47 (1H, dt, J=1.4Hz, 8.6Hz), 7.59 (1H, d, J=8.8Hz), 7.83 (2H, t, J=8.6Hz), 9.73 (1H, brs)

NMR (39) ($CDCl_3$) δppm: 2.24 (3H, s), 3.85 (3H, s), 4.75 (2H, s), 6.51 (1H, d, J=8.3Hz), 6.63 (1H, d, J=8.3Hz), 7.14 (1H, t, J=8.3Hz), 7.29-7.40 (1H, m), 7.40-7.52 (1H, m), 7.74-7.91 (2H, m)

NMR (40) ($CDCl_3$) δppm: 1.30 (3H, t, J=7Hz), 3.91 (3H, s), 4.27 (2H, q, J=7Hz), 4.63 (2H, s), 6.41 (1H, d, J=2.5Hz), 6.48 (1H, dd, J=2.5Hz, J=9Hz), 7.75 (1H, d, J=9Hz), 10.96 (1H, s)

NMR (41) ($CDCl_3$) δppm: 1.30 (3H, t, J=7Hz), 3.86 (3H, s), 3.89 (3H, s), 4.28 (2H, q, J=7Hz), 6.43 (1H, dd, J=2.5Hz, J=8.5Hz), 6.58 (1H, d, J=2.5Hz), 7.84 (1H, d, J=8.5Hz)

NMR (42) ($CDCl_3$) δppm: 1.69 (3H, d, J=7Hz), 3.80 (3H, s), 4.95 (1H, q, J=7Hz), 6.45-6.7 (3H, m), 7.15-7.5 (3H, m), 7.7-7.9 (2H, m), 9.77 (1H, br)

NMR (43) ($CDCl_3$) δppm: 3.38 (2H, d, J=6.5Hz), 3.84 (3H, s), 3.86 (3H, s), 4.74 (2H, s), 4.95-5.15 (2H, m), 5.85-6.1 (1H, m), 6.34 (1H, s), 7.69 (1H, s), 9.28 (1H, br)

NMR (44) ($CDCl_3$) δppm: 3.80 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 4.73 (2H, s), 5.98 (2H, br), 6.12 (1H, d, J=9Hz), 7.59 (1H, d, J=9.1Hz)

NMR (45) ($CDCl_3$) δppm: 2.88 (6H, s), 3.80 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 4.71 (2H, s), 6.48 (1H, d, J=8.7Hz), 7.29 (1H, d, J=8.7Hz)

NMR (46) ($CDCl_3$) δppm: 2.91 (6H, s), 3.88 (3H, s), 3.89 (3H, s), 4.80 (2H, s), 6.64 (1H, d, J=8.7Hz), 7.30-7.38 (2H, m), 7.42-7.51 (1H, m), 7.80-7.89 (2H, m), 10.24 (1H, br)

NMR (47) ($CDCl_3$) δppm: 2.90 (6H, s), 3.69 (3H, s), 3.74 (2H, d, J=21.7Hz), 3.75 (3H, s), 3.90 (3H, s), 4.83 (2H, s), 6.74 (1H, d, J=8.6Hz), 7.26 (1H, d, J=8.6Hz), 7.34 (1H, t, J=9.1Hz), 7.43 (1H, t, J=9.1Hz), 7.80-7.90 (2H, m), 10.10 (1H, br)

NMR (48) ($CDCl_3$) δppm: 3.86 (3H, s), 3.89 (3H, s), 4.65 (2H, s), 4.97 (1H, d, J=5.9Hz), 6.49-6.55 (2H, m), 7.34-7.54 (3H, m), 7.84-7.89 (1H, m), 7.98 (1H, d, J=7.3Hz)

NMR (49) ($CDCl_3$) δppm: 3.72 (3H, s), 3.78 (3H, s), 3.79 (2H, d, J=21.7Hz), 3.92 (3H, s), 4.66 (2H, s), 4.97 (2H, d, J=5.9Hz), 6.53-6.61 (2H, m), 7.39-7.54 (3H,

m), 7.82-7.90 (2H, m), 7.98 (1H, d, J=7.6Hz)

NMR (50) (DMSO-d_6) δppm: 1.13 (6H, d, J=7.0Hz), 3.08-3.35 (1H, m), 3.69 (3H, s), 4.66 (2H, s), 6.38 (1H, d, J=2.4Hz), 6.48 (1H, d, J=2.4Hz, J=8.4Hz), 7.07 (1H, d, J=8.4Hz), 12.93 (1H, s)

NMR (51) (DMSO-d_6) δppm: 0.69-1.00 (3H, m), 1.08-1.62 (8H, m), 2.32-2.63 (2H, m), 3.68 (3H, s), 4.65 (2H, s), 6.30-6.53 (2H, m), 7.00 (1H, d, J=8.2Hz), 12.92 (1H, s)

NMR (52) ($CDCl_3$) δppm: 2.31 (3H, s), 3.78 (3H, s), 4.74 (2H, s), 6.42 (1H, d, J=2.4Hz), 6.52 (1H, dd, J=2.4Hz, J=8.8Hz), 7.12 (1H, d, J=8.8Hz), 7.25-7.53 (2H, m), 7.72-7.94 (2H, m), 9.71 (1H, s)

NMR (53) ($CDCl_3$) δppm: 1.30 (6H, d, J=6.9Hz), 3.19-3.46 (1H, m), 3.79 (3H, s), 4.75 (2H, s), 6.44 (1H, d, J=2.4Hz), 6.60 (1H, dd, J=2.4Hz, J=8.5Hz), 7.20 (1H, d, J=8.5Hz), 7.24-7.53 (2H, m), 7.72-7.94 (2H, m), 9.51-9.82 (1H, brs)

NMR (54) ($CDCl_3$) δppm: 0.78-0.99 (3H, m), 1.18-1.77 (8H, m), 2.67 (2H, t, J=7.9Hz), 3.78 (3H, s), 4.74 (2H, s), 6.43 (1H, d, J=2.4Hz), 6.55 (1H, dd, J=2.4Hz, J=8.3Hz), 7.12 (1H, d, J=8.3Hz), 7.23-7.52 (2H, m), 7.75-7.92 (2H, m), 9.56-9.80 (1H, brs)

NMR (55) (DMSO-d_6) δppm: 2.09 (3H, s), 3.68 (3H, s), 4.66 (2H, s), 6.32-6.52 (2H, m), 7.02 (1H, d, J=8.1Hz), 12.95 (1H, s)

NMR (56) ($CDCl_3$) δppm: 3.82 (3H, s), 3.93 (3H, s), 4.73 (2H, s), 6.34 (1H, s), 8.02 (1H, s), 10.93 (1H, s)

NMR (57) ($CDCl_3$) δppm: 3.82, 3.86, 3.88 (each 3H, each s), 4.77 (2H, s), 6.40 (1H, s), 8.07 (1H, d, J=3.1Hz)

NMR (58) (DMSO-d_6) δppm: 3.74, 3.82 (each 3H, each s), 4.97 (2H, s), 6.74 (1H, s), 7.85 (1H, d, J=3.6Hz), 12.82-13.44 (1H, br)

NMR (59) (DMSO-d_6) δppm: 3.73, 3.74 (each 3H, each s), 4.63 (2H, s), 6.76 (1H, s), 7.30 (1H, s), 10.66 (1H, brs)

NMR (60) (DMSO-d_6) δppm: 3.66 (3H, s), 3.70 (3H, s), 4.64, 4.73 (total 1H, each s), 6.34-6.52 (2H, m), 6.79-6.96 (1H, m), 12.88-13.03 (1H, m)

NMR (61) ($CDCl_3$) δppm: 3.77 (3H, s), 3.97 (3H, s), 4.78 (2H, s), 6.51-6.72 (2H, m), 6.89 (1H, d, J=8.8Hz), 7.21-7.56 (2H, m), 7.73-7.92 (2H, m)

NMR (62) (DMSO-d_6) δppm: 1.27 (3H, t, J=7.0Hz), 3.65 (3H, s), 3.92 (2H, q, J=7.0Hz), 4.65 (2H, s), 6.32-6.52 (2H, m), 6.78-6.93 (1H, m), 12.81-13.01 (1H, brs)

NMR (63) ($CDCl_3$) δppm: 2.84 (6H, s), 3.89 (3H, s), 4.81 (2H, s), 5.23 (2H, s), 6.70 (1H, d, J=9.0Hz), 7.26-7.40 (5H, m), 7.60-7.64 (2H, m)

NMR (64) ($CDCl_3$) δppm: 2.91 (6H, s), 3.93 (3H, s), 4.73 (2H, s), 7.14 (1H, d, J=7.8Hz), 7.90-7.94 (2H, m), 9.72 (1H, br)

NMR (65) ($CDCl_3$) δppm: 3.03 (6H, s), 3.91 (3H, s), 4.92 (2H, s), 7.12 (1H, d, J=8.3Hz), 7.29 (1H, dt, J=1.2Hz, J=7.8Hz), 7.43 (1H, dt, J=1.2Hz, J=7.8Hz), 7.78-7.86 (4H, m), 13.22 (1H, br)

NMR (66) ($CDCl_3$) δppm: 3.03 (6H, s), 3.61 (2H, d, J=22.7Hz), 3.77 (3H, s), 3.81 (3H, s), 4.94 (2H, s), 7.15 (1H, d, J=8.4Hz), 7.30 (1H, t, J=7.8Hz), 7.43 (1H, t, J=7.8Hz), 7.76-7.86 (4H, m)

NMR (67) ($CDCl_3$) δppm: 3.96 (3H, s), 4.03 (3H, s), 4.55 (1H, brd, J=27.4Hz), 4.76 (2H, s), 6.71 (1H, d, J=8.7Hz), 7.25-7.38 (1H, m), 7.39-7.88 (19H,

m), 10.50 (1H, brs)

NMR (68) ($CDCl_3$) δppm: 2.10-2.30 (2H, m), 3.58 (2H, t, J=6.6Hz), 4.04-4.19 (2H, m), 4.38-4.72 (1H, m), 4.65 (2H, s), 6.39 (1H, dd, J=2.3Hz, J=8.6Hz), 6.52 (1H, d, J=2.3Hz), 7.28-7.95 (20H, m), 10.58 (1H, brs)

NMR (69) ($CDCl_3$) δppm: 1.82-2.11 (2H, m), 2.11-2.38 (4H, m), 2.3-2.62 (2H, m), 3.49-3.75 (4H, m), 4.04 (2H, t, J=5.9Hz), 4.50-4.93 (1H, m), 4.68 (2H, s), 6.40 (1H, dd, J=2.2Hz, J=8.6Hz), 6.54 (1H, d, J=2.2Hz), 7.23-7.37 (1H, m), 7.37-7.62 (10H, m), 7.62-7.96 (9H, m), 10.37 (1H, brs)

NMR (70) ($CDCl_3$) δppm: 3.00 (6H, s), 3.89 (3H, s), 4.70 (2H, s), 6.49 (1H, dd, J=2.5Hz, J=8.5Hz), 6.57 (1H, d, J=2.5Hz), 6.93 (1H, dd, J=2.5Hz, J=9Hz), 7.08 (1H, d, J=2.5Hz), 7.20-8.05 (16H, m), 8.55-8.65 (1H, m), 9.90 (1H, br)

NMR (71) ($CDCl_3$) δppm: 1.21-1.56 (2H, m), 1.67 (1H, br), 1.75-1.94 (2H, m), 2.01 (1H, t, J=10.6Hz), 2.01-2.89 (14H, m), 3.02-3.28 (2H, m), 3.55-3.78 (2H, m), 3.85-4.02 (1H, m)

NMR (72) ($CDCl_3$) δppm: 1.83 (1H, br), 2.15 (1H, dd, J=4.1Hz, J=12.8Hz), 2.26 (6H, s), 2.43 (1H, dd, J=7.8Hz, J=12.8Hz), 2.53 (1H, dd, J=10.2Hz, J=12.1Hz), 2.68-2.98 (3H, m), 3.50-3.72 (2H, m), 3.78-3.99 (1H, m)

NMR (73) ($CDCl_3$) δppm: 2.78 (2H, t, J=7.5Hz), 3.09 (2H, t, J=7.5Hz), 3.90 (3H, s), 7.15 (2H, d, J=8.5Hz), 7.25-7.45 (2H, m), 7.68 (1H, d, J=7.5Hz), 7.8-7.95 (1H, m), 7.90 (2H, d, J=8.5Hz)

NMR (74) ($CDCl_3$) δppm: 2.77 (2H, t, J=7.5Hz), 3.06 (2H, t, J=7.5Hz), 3.66 (2H, d, J=22.6Hz), 3.75 (3H, s), 3.81 (3H, s), 7.10-7.22 (2H, m), 7.26-7.49 (2H, m), 7.63-7.68 (1H, m), 7.81-7.90 (3H, m)

NMR (75) ($CDCl_3$) δppm: 2.79 (2H, t, J=7.5Hz), 3.06 (2H, t, J=7.5Hz), 3.76

(3H, s), 3.86 (3H, s), 6.65 (1H, d, J=8Hz), 6.72 (1H, s), 7.25-7.5 (2H, m), 7.6-7.75 (2H, m), 7.85 (1H, d, J=7.5Hz), 11.40 (1H, br)

NMR (76) ($CDCl_3$) δppm: 2.80 (2H, t, J=7.5Hz), 3.05 (2H, t, J=7.5Hz), 3.73 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 3.82 (2H, d, J=21.5Hz), 6.65-6.8 (2H, m), 7.25-7.45 (2H, m), 7.60 (1H, d, J=8.5Hz), 7.64 (1H, d, J=7.5Hz), 7.82 (1H, dd, J=1Hz, J=7.5Hz), 11.49 (1H, br)

NMR (77) ($CDCl_3$) δppm: 3.62 (2H, d, J=22.5Hz), 3.77, 3.82 (6H, each s), 4.04 (3H, s), 4.85 (2H, s), 7.02 (1H, d, J=8.5Hz), 7.3-7.55 (2H, m), 7.6-7.7 (2H, m), 7.8-7.9 (2H, m), 10.31 (1H, br)

Example 1

A solution of 2-(2-isopropylphenoxymethylcarbonylamino)benzothiazole (6.5 g), anhydrous maleic acid (3.9 g) and aluminum chloride (8.0 g) in 1,2-dichloroethane (50 ml) is stirred at room temperature for 7 hours. To the mixture is added water in order to decompose the aluminum chloride, and thereto is added ethyl acetate, and the mixture is stirred. The precipitated crystals are collected by filtration, washed with ethyl acetate, and dried to give a mixture (7.3 g) of a trans-compound and a cis-compound. The mixture thus obtained is dissolved in dimethylformamide (50 ml), and thereto is added conc. hydrochloric acid (1 ml), and the mixture is stirred at 60°C for 30 minutes. To the mixture is added water (about 100 ml), and the precipitated crystals are collected by filtration, washed with methanol, and dried to give 2-[2-isopropyl-4-(trans-3-carboxyacryloyl)phenoxymethylcarbonylamino]benzothiazole (6.2 g).

^{1}H-NMR (DMSO-d_6) δppm: 1.25 (6H, d, J=7Hz), 3.40 (1H, sept, J=7Hz), 5.12 (2H, s), 6.64 (1H, d, J=15.5Hz), 7.03 (1H, d, J=8.5Hz), 7.25-7.5 (2H, m), 7.77

(1H, d, J=7.5Hz), 7.85-8.05 (4H, m), 12.70 (1H, br), 13.10 (1H, br)

Example 2

To a solution of 2-[2-isopropyl-4-(3-carboxyacryloyl)phenoxymethylcarbonylamino]benzothiazole (1.0 g) and triethylamine (0.4 ml) in dichloromethane (20 ml) is added dropwise isobutyl chloroformate (0.32 ml) under ice-cooling. To the mixture is added N-methylpiperazine (0.27 ml) at the same temperature, and the mixture is stirred for 2.5 hours. The reaction solution is washed with water, dried and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; dichloromethane → dichloromethane:methanol = 30:1), and recrystallized from ethanol to give 2-{2-isopropyl-4-[3-(4-methyl-1-piperazinylcarbonyl)acryloyl]phenoxymethylcarbonylamino}benzothiazole (0.80 g).

Pale brown powder

M.p. 190-192°C

Example 3

A solution of 2-[4-(3-carboxyacryloyl)phenoxymethylcarbonyamino]-benzothiazole (1.0 g), thionyl chloride (0.23 ml) and a drop of dimethylformamide (20 ml) in dichloromethane (20 ml) is stirred at room temperature for 10 hours. The solution is added dropwise into a solution of 4-(4-methyl-1-piperazinyl)piperidine (0.5 g) and pyridine (1 ml) in dichloromethane (20 ml) under ice-cooling. To the reaction solution is added water, and the mixture is basified with 5 % aqueous sodium hydroxide solution. The mixture is extracted with dichloromethane, and the extract is washed, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; dichloromethane:methanol = 50:1 → 10:1). The compound thus

obtained is converted into a hydrochloride thereof by a conventional method and recrystallized from ethanol-diethyl ether to give 2-[4-{3-[4-(4-methyl-1-piperazinyl)-1-piperidinylcarbonyl)acryloyl}phenoxymethylcarbonylamino]-benzothiazole dihydrochloride (0.14 g).

White powder

M.p. 202.5-225°C (decomposed)

^{1}H-NMR (DMSO-d_6) δppm: 1.35-1.8 (2H, m), 2.0-2.3 (2H, m), 2.6-3.9 (11H, m), 2.81 (3H, s), 4.1-4.3 (1H, m), 4.5-4.7 (1H, m), 5.08 (2H, s), 7.15 (2H, d, J=9Hz), 7.3-7.55 (3H, m), 7.76 (1H, d, J=14Hz), 7.77 (1H, d, J=8.5Hz), 7.98 (1H, d, J=8Hz), 8.05 (2H, d, J=9Hz), 12.67 (1H, br)

Example 4

To a solution of 2-[2-isopropyl-4-(3-carboxyacryloyl)phenoxymethyl-carbonylamino]benzothiazole (0.97 g) in dimethylformamide (10 ml) are added dropwise 4-(4-methyl-1-piperazinyl)piperidine (0.65 g) and diethyl cyano-phosphate (0.6 ml) at room temperature. To the mixture is added triethylamine (0.5 ml), and the mixture is stirred at room temperature for 10 minutes. To the mixture is added water, and the mixture is extracted with ethyl acetate. The extract is washed with water, dried, and concentrated under reduced pressure. The residue is purified by silica gel column chromatography (solvent; dichloro-methane:methanol = 100:1 → 10:1). The compound thus obtained is converted into a hydrochloride thereof in ethanol by a conventional method, and recrystallized from ethanol-diethyl ether to give 2-{2-isopropyl-4-[3-[4-(4-methyl-1-piperazinyl)-1-piperidinylcarbonyl]acryloyl]phenoxymethylcarbonylamino}-benzothiazole dihydrochloride (0.45 g).

Yellow powder

M.p. 186-190°C (decomposed)

Example 5

To a solution of dibutyl tartrate (4.0 g) in methanol (100 ml) is added a solution of sodium periodate (3.0 g) in water (30 ml), and the mixture is stirred for 10 minutes, and extracted with ethyl acetate. Separately, to a suspension of dimethyl {[3-methoxy-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]-methyl}phosphonate (5.7 g) in tetrahydrofuran (100 ml) is added a 5 % aqueous sodium hydroxide solution under ice-cooling until the reaction solution becomes uniform, and then thereto is added dropwise a solution of glyoxalate, which is previously prepared from dibutyl tartrate, in tetrahydrofuran (30 ml) under ice-cooling. The mixture is stirred for 30 minutes, and acidified with 5 % hydrochloric acid, and concentrated under reduced pressure to remove the tetrahydrofuran. The precipitated crystals are collected by filtration, and washed with dichloro-methane. The dichloromethane layer is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; dichloro-methane:methanol = 200:1) to give 2-[2-methoxy-4-(3-butoxycarbonylacryloyl)-phenoxymethylcarbonylamino]benzothiazole (2.85 g), which is further stirred in tetrahydrofuran-5 % aqueous sodium hydroxide solution at room temperature for 30 minutes to give 2-[2-methoxy-4-(3-carboxyacryloyl)phenoxymethylcarbonyl-amino]benzothiazole (2.9 g).

^{1}H-NMR (DMSO-d_6) δppm: 3.89 (3H, s), 5.09 (2H, s), 6.67 (1H, d, J=15.5Hz), 7.08 (1H, d, J=8.5Hz), 7.25-7.55 (2H, m), 7.57 (1H, m), 7.7-8.1 (4H, m), 11.68 (1H, br)

Example 6

To a solution of ethyl propiolate (17.7 ml) in tetrahydrofuran (450 ml) is added dropwise a 1.71M solution of n-butyl lithium in n-hexane (102 ml) at −78°C, and the mixture is stirred for 10 minutes. To the solution is added dropwise a solution of 2-(2-methoxy-4-formylphenoxymethylcarbonylamino)-benzothiazole (20 g) in tetrahydrofuran (400 ml) and N,N-dimethylpropylene urea (40 ml) at the same temperature over a period of 15 minutes. The mixture is further stirred for 10 minutes, and the reaction vessel is taken out from an iced bath, and further stirred for 20 minutes. To the mixture is added acetic acid (11 ml), and the mixture is diluted with ethyl acetate. The ethyl acetate layer is washed with a saturated aqueous sodium carbonate solution, dried over sodium sulfate, and concentrated. The residue is purified by silica gel column chromatography (solvent; dichloromethane : methanol = 100:1 → 50:1) to give 2-[2-methoxy-4-(3-methoxycarbonyl-1-hydroxypropargyl)phenoxymethyl-carbonylamino]benzothiazole (33.7 g) as a dark brown oil.

To a solution of 2-[2-methoxy-4-(3-methoxycarbonyl-1-hydroxy-propargyl)phenoxymethylcarbonylamino]benzothiazole (33.7 g) in dimethyl-formamide (150 ml) is added tri-n-butylamine (14.3 ml), and the mixture is stirred at room temperature for 1.5 hour. The mixture is diluted with ethyl acetate, and washed with 0.15N hydrochloric acid, and dried over sodium sulfate. The mixture is concentrated under reduced pressure to remove the solvent, and the precipitated crystals are collected by filtration to give 2-[2-methoxy-4-(trans-3-methoxycarbonylacryloyl)phenoxymethylcarbonylamino]benzothiazole (Compound A, 5.5 g) as pale yellow powder. On the other hand, the filtrate is concentrated under reduced pressure, and crystallized from ethanol-diethyl ether

to give 2-[2-methoxy-4-(cis-3-methoxycarbonylacryloyl)phenoxymethylcarbonylamino]benzothiazole (Compound B, 6.0 g) as pale yellow powder.

Compound A:

^{1}H-NMR (DMSO-d_6) δppm: 1.26 (3H, t, J=7.1Hz), 3.92 (3H, s), 4.21 (2H, q, J=7.1Hz), 5.11 (2H, s), 6.71 (1H, d, J=15.5Hz), 7.08 (1H, d, J=8.6Hz), 7.31-7.37 (1H, m), 7.44-7.50 (1H, m), 7.59 (1H, d, J=2.0Hz), 7.75-7.81 (2H, m), 7.98 (1H, d, J=15.5Hz), 8.00-8.02 (1H, m), 12.67 (1H, brs)

Compound B:

^{1}H-NMR (DMSO-d_6) δppm: 1.05 (3H, t, J=7.1Hz), 3.89 (3H, s), 3.97 (2H, q, J=7.1Hz), 5.11 (2H, s), 6.35 (1H, d, J=12.3Hz), 7.05 (1H, d, J=8.8Hz), 7.21 (1H, d, J=12.3Hz), 7.31-7.37 (1H, m), 7.44-7.50 (3H, m), 7.78-7.81 (1H, m), 7.99-8.02 (1H, m), 12.62 (1H, brs)

Example 7

A solution of 2-{2-isopropyl-4-[trans-3-(4-methyl-1-piperazinyl)-carbonylacryloyl]phenoxymethylcarbonylamino}benzothiazole (100 mg) in dimethylformamide (10 ml) is allowed to stand for 6.5 hours by a window in order to be exposed to direct sunlight. To the mixture is added water, the precipitated crystals are collected by filtration, and recrystallized from ethanol to give 2-{2-isopropyl-4-[cis-3-(4-methyl-1-piperazinyl)carbonylacryloyl]phenoxymethylcarbonylamino}benzothiazole (45 mg).

Pale yellow powder

M.p. 114-115°C

Example 8

To a solution of dimethyl {[3-methoxy-4-(2-benzothiazolylaminocarbonylmethoxy)benzoyl]methyl}phosphonate (1.7 g) and pyridine-4-aldehyde (0.5 g) in tetrahydrofuran (30 ml) is added a 5% aqueous sodium hydroxide solution (6 ml) under ice-cooling, and the mixture is stirred for 5 hours. The mixture is neutralized with acetic acid, and the precipitated crystals are collected by filtration, and then recrystallized from dichloromethane-ethanol-diethyl ether to give 2-{2-methoxy-4-[3-(4-pyridyl)acryloyl]phenoxymethylcarbonylamino}-benzothiazole (1.3 g).

Pale yellow powder

M.p. 206-207°C

Example 9

To a solution of 2-[2-methoxy-4-(3-t-butoxycarbonyl-1-hydoxypropargyl)-phenoxymethylcarbonylamino]benzothiazole (1 g) in chloroform (50 ml) is added active manganese dioxide (1 g), and the mixture is refluxed for two hours. To the mixture is further added active manganese dioxide (1 g), and the mixture is refluxed for 1.5 hour. The mixture is filtered through a cerite pad, and the filtrate is concentrated. The residue is recrystallized from ethanol to give 2-[2-methoxy-4-(3-t-butoxycarbonylpropiolyl)phenoxymethylcarbonylamino]benzothiazole (0.5 g).

Example 10

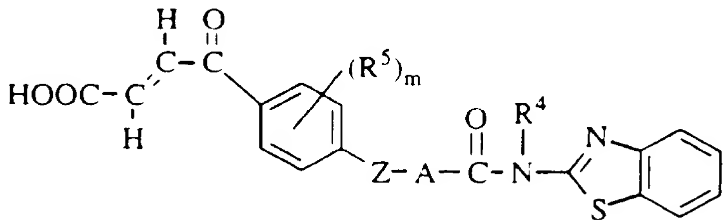
To a solution of 2-[2-methoxy-4-(3-t-butoxycarbonylpropioloyl)phenoxymethylcarbonylamino]benzothiazole (0.5 g) in methylene chloride (30 ml) is added trifluoroacetic acid (10 ml), and the mixture is stirred at room temperature for 4 hours. The mixture is concentrated, and to the residue is added methylene chloride. The mixture is stirred, and the precipitated crystals are collected by

filtration, and recrystallized from dichloromethane-trifluoroacetic acid to give 2-[2-methoxy-4-(3-carboxypropioloyl)phenoxymethylcarbonylamino]-benzothiazole (0.26 g) as brown powder.

M.p. 174-176°C

Using the suitable starting compounds, the following compounds are obtained in the same manner as in Example 1 or 5.

Table 38



Example 11

R^4: H A: $-CH_2-$ Z: O

R^5: CH_3 (2-position) m: 1

M.p. 261-262°C Crystalline form: Beige powder

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 12

R^4: H A: $-CH_2-$ Z: O

R^5: C_2H_5 (2-position) m: 1

M.p. 245-246°C Crystalline form: Beige powder

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 13

R^4: H A: $-CH_2-$ Z: O

R^5: n-Propyl (2-position) m: 1

Crystalline form: Yellow powder Form: Free

NMR (1)

Table 39

Example 14

R^4: H A: $-CH_2-$ Z: O

R^5: Isopropyl (2-position) m: 1

M.p. 225-240°C (decomp.) Crystalline form: Yellow powder NMR (2)

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 15

R^4: H A: $-CH_2-$ Z: O

R^5: n-Butyl (2-position) m: 1

M.p. 187.5-190°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform-dimethylformamide

Form: Free

Example 16

R^4: H A: $-CH_2-$ Z: O

R^5: H m: 1

M.p. 250-275°C (decomp.) Crystalline form: White powder NMR (3)

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 17

R^4: H A: $-CH_2-$ Z: O

R^5: n-Pentyl (2-position) m: 1

M.p. 139-163°C Crystalline form: Pale yellow powder NMR (4)

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Table 40

Example 18

R^4: H A: $-CH_2-$ Z: O

R^5: F (2-position) m: 1

M.p. 233-234°C Crystalline form: Pale brown powder

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 19

R^4: H A: $-CH_2-$ Z: O

R^5: Cl (2-position) m: 1

Crystalline form: Yellow powder

Form: Free NMR (5)

Example 20

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_4$ (combined at 2- and 3-positions) m: 2

Crystalline form: Yellow powder NMR (6)

Form: Free

Example 21

R^4: H A: $-CH_2-$ Z: O

R^5: CH_3 (2-and 3-positions) m: 2

Crystalline form: Yellow powder NMR (7)

Form: Free

Table 41

Example 22

R^4: H A: $-CH_2-$ Z: O

R^5: CH_3 (2- and 6-positions) m: 2

Crystalline form: Beige powder NMR (8)

Solvent for recrystallization: Dimethylformamide-methanol

Form: Free

Example 23

R^4: H A: $-CH_2-$ Z: O

R^5: CH_3 (3- and 5-positions) m: 2

Crystalline form: Yellow powder Form: Free

NMR (9)

Example 24

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2CO_2C_2H_5$ (2-position) m: 1

M.p. 199.6-203.8°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform-dimethylformamide

Form: Free

Example 25

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_4OCOCH_3$ (2-position) m: 1

M.p. 176-177.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform Form: Free

Table 42

Example 26

R^4: H   A: $-CH_2-$ Z: O

R^5: C_2H_5O (2-position)   m: 1

Crystalline form: Yellow powder   NMR (10)

Form: Free

Example 27

R^4: H   A: $-CH_2-$ Z: O

R^5: CH_3 (3-position)   m: 1

M.p. 290°C (decomp.)   Crystalline form: White needles   NMR (11)

Solvent for recrystallization: Dimethylformamide   Form: Free

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Example 28

R^4: H   A: $-CH_2-$ Z: O

R^5: C_2H_5 (3-position)   m: 1

Crystalline form: Yellow powder   NMR (12)

Form: Free

Example 29

R^4: H   A: $-CH_2-$ Z: O

R^5: n-Propyl (3-position)   m: 1

M.p. 282°C (decomp.)   Crystalline form: Pale brown needles

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Table 43

Example 31

R^4: H A: $-CH_2-$ Z: O

R^5: n-Butyl (3-position) m: 1

M.p. 267-279°C (decomp.) Crystalline form: Pink powder

Form: Free NMR (14)

Example 32

R^4: H A: $-CH_2-$ Z: O

R^5: Isopropyl (3-position) m: 1

M.p. 262.5-265.5°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Example 33

R^4: H A: $-CH_2-$ Z: O

R^5: Cl (3-position) m: 1

Crystalline form: Pale yellow powder NMR (15)

Form: Free

Table 44

Example 34

R^4: H A: $-CH_2-$ Z: O

R^5: F (3-position) m: 1

Crystalline form: Pale yellow powder NMR (16)

Form: Free

Example 35

R^4: H A: $-CH_2-$ Z: O

R^5: CH_3O (3-position) m: 1

Crystalline form: Yellow powder NMR (17)

Form: Free

Example 36

R^4: H A: $-CH_2-$ Z: O

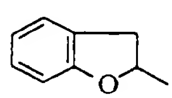
R^5: C_2H_5O (3-position) m: 1

Crystalline form: Yellow powder NMR (18)

Form: Free

Example 37

R^4: H m: 1 Z: O

R^5 and A combine to form: 

M.p. 294-295°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Dimethylformamide Form: Free

Table 45

Example 38		
R^4: H	A: $-CH_2-$	Z: O
R^5: CH_3O (2-position)		m: 1
Crystalline form: Yellow powder		NMR (19)
Form: Free		
Example 39		
R^4: H	A: $-CH_2-$	Z: O
R^5: $(CH_3)_2CHO-$ (3-position)		m: 1
Crystalline form: Pale yellow powder		NMR (20)
Form: Free		
Example 40		
R^4: H	A: $-CH_2-$	Z: O
R^5: CF_3CH_2O- (3-position)		m: 1
Crystalline form: Pale yellow powder		NMR (21)
Form: Free		
Example 41		
R^4: H	A: $-CH_2-$	Z: O
R^5: CF_3 (2-position)		m: 1
Crystalline form: Colorless powder		NMR (22)
Form: Free		

Table 46

Example 42

R^4: H A: $-CH_2-$ Z: O

R^5: $-OCH_2CON(C_2H_5)_2$ (2-position) m: 1

Crystalline form: Yellow powder NMR (23)

Form: Free

Example 43

R^4: H A: $-CH_2-$ Z: O

R^5: $-COOCH_3$ (2-position) m: 1

Crystalline form: Pale yellow powder NMR (24)

Form: Free

Example 44

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2-CONH-$ (combined at 2- and 3-positions) m: 2

Crystalline form: Yellow powder NMR (25)

Form: Free

Example 45

R^4: H A: $-CH_2-$ Z: O

R^5: $(CH_3)_3C-$ (2-position) m: 1

M.p. 263-266°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Table 47

Example 46

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2COOCH_3$ (2-position) m: 1

Crystalline form: Yellow powder NMR (26)

Form: Free

Example 47

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2CON(CH_3)_2$ (2-position) m: 1

Crystalline form: Pale yellow powder NMR (27)

Form: Free

Example 48

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2CON(C_2H_5)_2$ (2-position) m: 1

Crystalline form: Yellow amorphous NMR (28)

Form: Free

Example 49

R^4: H A: $-CH_2-$ Z: O

R^5: Cl (2-position) m: 1

M.p. 235.5-237°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-water

Form: Free

Table 48

Example 50

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_2COOC_2H_5$ (2-position) m: 1

M.p. 199.6-203.8°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform-dimethylformamide

Form: Free NMR (29)

Example 51

R^4: H A: $-CH_2-$ Z: O

R^5: n-Butyl (2-position) m: 1

M.p. 187.5-190°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform-dimethylformamide

Form: Free

Example 52

R^4: H A: $-CH_2-$ Z: O

R^5: $-(CH_2)_4OCOCH_3$ (2-position) m: 1

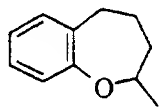
M.p. 176-177.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform Form: Free

Table 49

Example 53

R^4: H m: 1 Z: O

R^5 and A combine to form: 

M.p. 285-287°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Dimethylformamide-water

Form: Free

Example 54

R^4: H A: $-CH_2-$ Z: O

R^5: n-Heptyl (2-position) m: 1

M.p. 187-188.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-dimethylformamide

Form: Free

Example 55

R^4: H A: $-CH_2-$ Z: S

R^5: CH_3O (2-position) m: 1

M.p. 241-244°C Crystalline form: Yellow powder

Form: Free

^{1}H-NMR spectrum (NMR (1) to NMR (29)) as described in Tables 38-49 are as follows:

NMR (1) (DMSO-d_6) δppm: 0.92 (3H, t, J=7.4Hz), 1.58-1.69 (2H, m), 2.69 (2H, t, J=7.4Hz), 5.12 (2H, s), 6.65 (1H, d, J=15.4Hz), 7.03 (1H, d, J=8.6Hz), 7.31 (1H, t, J=7.6Hz), 7.44 (1H, t, J=7.7Hz), 7.76 (1H, d, J=7.7Hz), 7.87-7.99 (4H, m)

NMR (2) (DMSO-d_6) δppm: 1.25 (6H, d, J=7Hz), 3.40 (1H, sept, J=7Hz), 5.12 (2H, s), 6.64 (1H, d, J=15.5Hz), 7.03 (1H, d, J=8.5Hz), 7.25-7.5 (2H, m), 7.77 (1H, d, J=7.5Hz), 7.85-8.05 (4H, m), 12.70 (1H, br), 13.10 (1H, br)

NMR (3) (DMSO-d_6) δppm: 5.07 (2H, s), 6.65 (1H, d, J=15.5Hz), 7.15 (2H, d, J=9Hz), 7.1-7.5 (2H, m), 7.76 (1H, d, J=7Hz), 7.89 (1H, d, J=15.5Hz), 7.99 (1H, d, J=7Hz), 8.05 (2H, d, J=9Hz), 12.70 (1H, br), 13.04 (1H, br)

NMR (4) (DMSO-d_6) δppm: 0.89 (3H, t, J=6.4Hz), 1.21-1.50 (4H, m), 1.53-1.79 (2H, m), 2.69 (2H, t, J=8.0Hz), 5.14 (2H, s), 6.64 (1H, d, J=15.5Hz), 7.04 (1H, d, J=8.5Hz), 7.30-7.38 (1H, m), 7.43-7.51 (1H, m), 7.78-7.82 (1H, d, J=7.9Hz), 7.85-8.10 (4H, m)

NMR (5) (DMSO-d_6) δppm: 5.22 (2H, s), 6.67 (1H, d, J=15.5Hz), 7.24-7.49 (3H, m), 7.77 (1H, d, J=7.6Hz), 7.89 (1H, d, J=15.5Hz), 7.96-8.12 (3H, m), 12.83 (1H, br)

NMR (6) (DMSO-d_6) δppm: 1.6-1.9 (4H, m), 2.65-3.0 (4H, m), 5.06 (2H, s), 6.45 (1H, d, J=16Hz), 6.82 (1H, d, J=8.5Hz), 7.25-7.65 (4H, m), 7.75 (1H, d, J=8Hz), 7.97 (1H, d, J=8Hz), 12.85 (1H, br)

NMR (7) (DMSO-d_6) δppm: 2.22 (3H, s), 2.31 (3H, s), 5.05 (2H, s), 6.44 (1H, d, J=15.5Hz), 6.85 (1H, d, J=8.5Hz), 7.25-7.6 (4H, m), 7.76 (1H, d, J=8Hz), 7.98

(1H, d, J=8Hz), 12.83 (1H, br)

NMR (8) (DMSO-d_6) δppm: 2.36 (6H, s), 4.75 (2H, s), 6.67 (1H, d, J=15.5Hz), 7.30-7.53 (2H, m), 7.77 (1H, d, J=8.9Hz), 7.79 (2H, s), 7.91 (1H, d, J=15.5Hz), 8.00 (1H, d, J=7.00Hz), 12.09-13.2 (2H, br)

NMR (9) (DMSO-d_6) δppm: 2.10 (6H, s), 4.95 (2H, s), 6.22 (1H, d, J=16Hz), 6.78 (2H, s), 7.02 (1H, d, J=16Hz), 7.25-7.5 (2H, m), 7.76 (1H, d, J=8Hz), 7.98 (1H, d, J=7.5Hz), 12.9 (2H, br)

NMR (10) ($CDCl_3$) δppm: 1.37 (3H, d, J=7.0Hz), 4.14 (2H, q, J=7.0Hz), 5.09 (2H, s), 6.65 (1H, d, J=15.5Hz), 7.06 (1H, d, J=8.6Hz), 7.31 (1H, d, J=7.4Hz), 7.44 (1H, t, J=7.4Hz), 7.55 (1H, s), 7.67-7.78 (2H, m), 7.90 (1H, d, J=15.5Hz), 7.98 (1H, d, J=7.4Hz), 12.74 (2H, br)

NMR (11) (DMSO-d_6) δppm: 2.45 (3H, s), 5.03 (2H, s), 6.45 (1H, d, J=15.6Hz), 6.90-7.06 (2H, m), 7.28-7.35 (1H, m), 7.41-7.48 (1H, m), 7.56 (1H, d, J=15.6Hz), 7.75 (2H, t, J=7.4Hz), 7.97-8.00 (1H, m), 12.80 (2H, brs)

NMR (12) (DMSO-d_6) δppm: 1.13 (3H, t, J=7.4Hz). 2.80 (2H, q, J=7.4Hz), 5.03 (2H, s), 6.47 (1H, d, J=15.6Hz), 6.94 (1H, dd, J=2.5Hz, J=8.6Hz), 7.01 (1H, d, J=2.5Hz), 7.27-7.50 (2H, m), 7.53 (1H, t, J=15.6Hz), 7.68-7.81 (2H, m), 7.92-8.03 (1H, m), 12.86 (2H, br)

NMR (14) (DMSO-d_6) δppm: 0.82 (3H, t, J=7.2Hz), 1.17-1.40 (2H, m), 1.40-1.61 (2H, m), 2.72-2.90 (2H, m), 5.06 (2H, s), 6.46 (1H, d, J=15.7Hz). 6.91-7.07 (2H, m), 7.30-7.41 (1H, m), 7.41-7.54 (1H, m), 7.51 (1H, d, J=15.7Hz), 7.74-7.82 (2H, m), 8.00-8.04 (1H, m)

NMR (15) (DMSO-d_6) δppm: 5.08 (2H, s), 6.50 (1H, d, =15.7Hz), 7.13 (1H, dd, J=2.5Hz, J=8.7Hz), 7.27-7.49 (4H, m), 7.71 (1H, d, J=8.7Hz), 7.76 (1H, d,

J=7.0Hz), 7.99 (1H, d, J=7.0Hz), 12.85 (1H, br)

NMR (16) (DMSO-d_6) δppm: 5.09 (2H, s), 6.61 (1H, d, J=15.6Hz), 6.98-7.13 (2H, m), 7.30 (1H, t, J=7.1Hz), 7.44 (1H, t, J=7.1Hz), 7.63 (1H, dd, J=3.4Hz, J=15.6Hz), 7.74-7.90 (2H, m), 7.97 (1H, d, J=7.1Hz), 12.88 (1H, br)

NMR (17) (DMSO-d_6) δppm: 3.89 (3H, s), 5.06 (2H, s), 6.51 (1H,d, J=15.5Hz), 6.71 (1H, d, J=2.2Hz, J=8.7Hz), 6.82 (1H, d, J=2.2Hz), 7.25-7.50 (2H, m), 7.66 (1H, d, J=8.7Hz), 7.70 (1H, d, J=15.5Hz), 7.74-7.81 (1H, m), 7.94-8.03 (1H, m), 12.80 (2H, br)

NMR (18) (DMSO-d_6) δppm: 1.34 (3H, t, J=6.9Hz), 4.15 (2H, q, J=6.9Hz), 5.05 (2H, s), 6.45 (1H, d, J=15.5Hz), 6.68 (1H, dd, J=2.0Hz, J=8.7Hz), 6.77 (1H, d, J=2.0Hz), 7.26-7.50 (2H, m), 7.66 (1H, d, J=8.7Hz), 7.72-7.81 (1H, m), 7.79 (1H, d, J=15.5Hz), 7.91-8.05 (1H, m), 12.77 (2H, br)

NMR (19) (DMSO-d_6) δppm: 3.89 (3H, s), 5.09 (2H, s), 6.67 (1H, d, J=15.5Hz), 7.08 (1H, d, J=8.5Hz), 7.25-7.55 (2H, m), 7.57 (1H, m), 7.7-8.1 (4H, m), 11.68 (1H, br)

NMR (20) (DMSO-d_6) δppm: 1.29 (6H, d, J=6.0Hz), 4.82 (1H, sept, J=6.0Hz), 5.05 (2H, s), 6.43 (1H, d, J=15.5Hz), 6.89 (1H, dd, J=2.3Hz, J=8.7Hz), 6.78 (1H, d, J=2.3Hz), 7.31 (1H, t, J=7.0Hz), 7.45 (1H, t, J=7.0Hz), 7.66 (1H, d, J=8.7Hz), 7.78 (1H, d, J=15.5Hz), 7.80 (1H, d, J=7.0Hz), 7.99 (1H, d, J=7.0Hz), 12.76 (1H, br)

NMR (21) (DMSO-d_6) δppm: 4.92 (2H, q, J=8.7Hz), 5.07 (2H, s), 6.48 (1H, d, J=15.5Hz), 6.81 (1H, dd, J=2.3Hz, J=8.8Hz), 6.93 (1H, d, J=2.3Hz), 7.32 (1H, t, J=7.0Hz), 7.45 (1H, t, J=7.0Hz), 7.62-7.79 (3H, m), 7.99 (1H, d, J=7.0Hz), 12.78 (1H, br)

NMR (22) ($DMSO-d_6$) δppm: 5.28 (2H, s), 6.69 (1H, d, J=15.5Hz), 7.25-7.55 (3H, m), 7.77 (1H, d, J=8Hz), 7.92 (1H, d, J=15.5Hz), 7.98 (1H, d, J=7.5Hz), 8.15-8.45 (2H, m), 12.88 (1H, br)

NMR (23) ($DMSO-d_6$) δppm: 1.03 (3H, t, J=7Hz), 1.18 (3H, t, J=7Hz), 3.1-3.5 (4H, m), 4.96 (2H, s), 5.10 (2H, s), 6.63 (1H, d, J=15.5Hz), 7.10 (1H, d, J=8.5Hz), 7.25-7.55 (3H, m), 7.7-7.85 (2H, m), 7.86 (1H, d, J=15.5Hz), 7.98 (1H, d, J=7.5Hz), 12.66 (1H, br)

NMR (24) ($DMSO-d_6$) δppm: 3.90 (3H, s), 5.18 (2H, s), 6.67 (1H, d, J=15.5Hz), 7.28-7.36 (2H, m), 7.46 (1H, t, J=7.6Hz), 7.78 (1H, d, J=7.6Hz), 7.89 (1H, d, J=15.5Hz), 7.99 (1H, t, J=7.6Hz), 8.25 (1H, dd, J=2.3Hz, J=8.9Hz) 8.38 (1H, d, J=2.3Hz)

NMR (25) ($DMSO-d_6$) δppm: 2.48 (2H, t, J=7.5Hz), 3.12 (2H, t, J=7.5Hz), 5.04 (2H, s), 6.52 (1H, d, J=15.7Hz), 7.13 (1H, d, J=8.7Hz), 7.34 (1H, t, J=7.2Hz), 7.42-7.63 (3H, m), 7.80 (1H, d, J=7.6Hz), 8.02 (1H, d, J=7.2Hz), 10.33 (1H, br), 12.98 (1H, br)

NMR (26) ($DMSO-d_6$) δppm: 2.71 (2H, t, J=7.6Hz), 2.98 (2H, t, J=7.6Hz), 3.59 (3H, s), 5.13 (2H, s), 6.60-6.75 (1H, m), 7.04-7.08 (1H, m), 7.27-7.38 (1H, m), 7.38-7.51 (1H, m), 7.55-7.78 (1H, m), 7.84-7.99 (4H, m), 9.40 (2H, brs)

NMR (27) ($DMSO-d_6 + CDCl_3$) δppm: 2.66 (2H, t, J=8.8Hz), 2.84 (3H, s), 2.89-3.06 (5H, m), 5.01 (2H, s), 6.57-6.75 (1H, m), 6.90-7.10 (1H, m), 7.18-7.30 (1H, m), 7.30-7.41 (1H, m), 7.63-7.72 (1H, m), 7.72-7.90 (3H, m), 7.96 (1H, s), 11.50-13.00 (2H, brs)

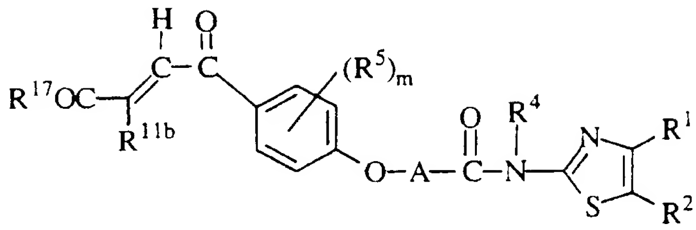
NMR (28) ($DMSO-d_6$) δppm: 1.00 (3H, t, J=7.0Hz), 1.07 (3H, t, J=7.0Hz), 2.68 (2H, t, J=7.4Hz), 3.01 (2H, t, J=7.4Hz), 3.15-3.46 (4H, m), 5.06 (2H, s), 6.78

(2H, d, J=15.4Hz), 6.95-6.99 (1H, m), 7.25-7.30 (1H, m), 7.38-7.43 (1H, m), 7.72-7.85 (5H, m)

NMR (29) (DMSO-d_6) δppm: 1.12 (3H, t, J=7.1Hz), 2.69 (2H, t, J=7.8Hz), 2.98 (2H, t, J=7.8Hz), 4.00 (2H, q, J=7.1Hz), 5.13 (2H, s), 6.61 (1H, d, J=15.4Hz), 7.04 (1H, d, J=8.8Hz), 7.30-7.40 (1H, m), 7.55 (1H, m), 7.75 (1H, d, J=7.3Hz), 7.86 (1H, d, J=15.4Hz), 7.91-8.10 (3H, m), 12.40-13.30 (2H, m)

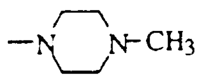
Using the suitable starting compounds, the compounds as listed in Tables 50-125 are obtained in the same manner as in Example 3 or 4.

Table 50



Example 56

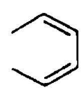
R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

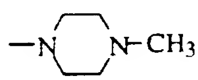
R^{11b}: H R^{17}:  R^5: H

M.p. 175-185°C Crystalline form: White powder

Solvent for recrystallization: Ethanol Form: Free NMR (1)

Example 57

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

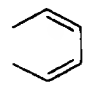
R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

M.p. 190-192°C Crystalline form: Pale brown powder

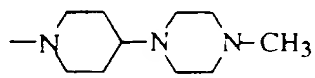
Solvent for recrystallization: Ethanol Form: Free Trans-form

Table 51

Example 58

R^1
: 
R^2

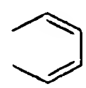
R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: H

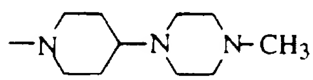
M.p. 202.5-225°C (decomp.) Crystalline form: White powder NMR (2)

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

Example 59

R^1
: 
R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

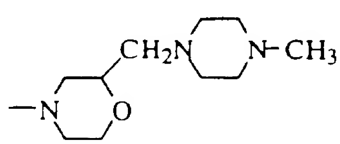
M.p. 186-190°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

Example 60

R^1
: 
R^2

R^4: H A: $-CH_2-$ m: 1

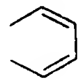
R^{11b}: H R^{17}:  R^5: H

M.p. 202-206°C (decomp.) Crystalline form: Yellow powder Form: 2HCl

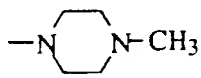
Solvent for recrystallization: Ethanol-diethyl ether

Table 52

Example 61

R^1 :  R^2

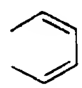
R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

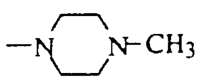
M.p. 114-115°C Crystalline form: Pale yellow powder Cis-form

Solvent for recrystallization: Ethanol-water Form: Free

Example 62

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Cl (2-position)

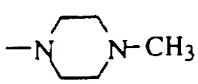
M.p. 206.5-209°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: Free

Example 63

R^1: CH_3 R^4: H A: $-CH_2-$ m: 1

R^2: H

R^{11b}: H R^{17}:  R^5: H

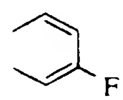
M.p. 138.5-141.5°C Crystalline form: White powder

Form: Free

Table 53

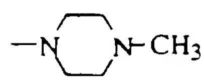
Example 64

R^1 : R^2



R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:



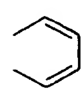
R^5: H

M.p. 221-222.5°C   Crystalline form: Pale yellow powder

Form: Free

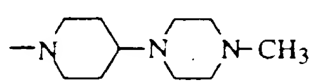
Example 65

R^1 : R^2



R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:



R^5: Cl (2-position)

M.p. 181-183°C   Crystalline form: White powder

Solvent for recrystallization: Ethanol-diethyl ether   Form: Free

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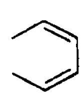
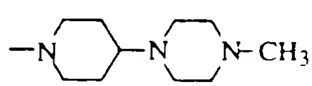
Example 66

R^1 : R^2



R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:



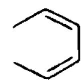
R^5: CH_3 (2-position)

M.p. 261-26[illegible]°C   Crystalline form: Yellow powder

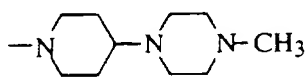
Solvent for recrystallization: Ethanol   Form: 2HCl

Table 54

Example 67

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

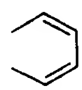
R^{11b}: H R^{17}: 

R^5: C_2H_5 (2-position)

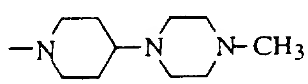
M.p. 227-229°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: 2HCl

Example 68

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

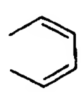
R^{11b}: H R^{17}: 

R^5: F (2-position)

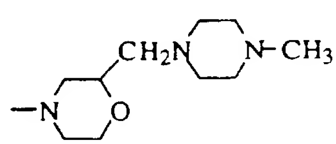
M.p. 226-227°C Crystalline form: Brown powder

Solvent for recrystallization: Ethanol Form: 2HCl

Example 69

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

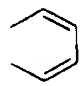
R^5: CH_3 (2-position)

Solvent for recrystallization: Ethanol Crystalline form: Pale yellow powder

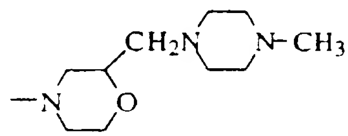
Form: 3HCl NMR (3)

Table 55

Example 70

R^1 :  R^4: H A: $-CH_2-$ m: 1

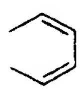
R^2

R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

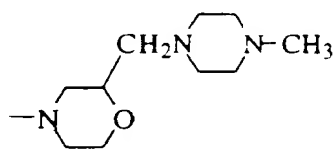
M.p. 157-160°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: 3HCl

Example 71

R^1 :  R^4: H A: $-CH_2-$ m: 1

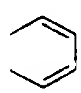
R^2

R^{11b}: H R^{17}:  R^5: F (2-position)

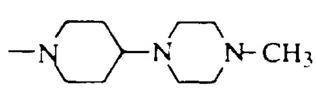
Solvent for recrystallization: Ethanol Crystalline form: Brown powder

Form: 3HCl NMR (4)

Example 72

R^1 :  R^4: H A: $-CH_2-$ m: 1

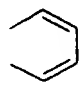
R^2

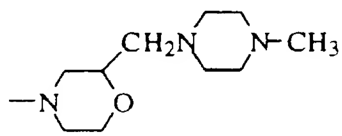
R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

Crystalline form: Yellow powder Form: 3HCl NMR (5)

Table 56

Example 73

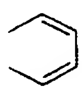
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

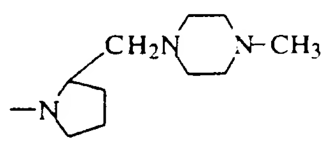
R^{11b}: H R^{17}:  R^5: Cl (2-position)

M.p. 200°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 74

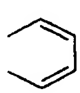
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

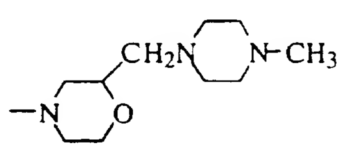
R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

M.p. 115-118°C Crystalline form: Pale beige powder

Solvent for recrystallization: Ethanol Form: 2HCl

Example 75

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

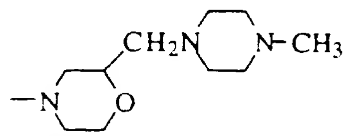
M.p. 188-191°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether

Table 57

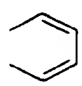
Example 76

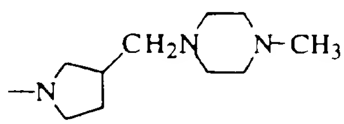
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

Crystalline form: Pale yellow powder Form: 3HCl NMR (6)

Example 77

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

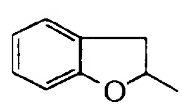
R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

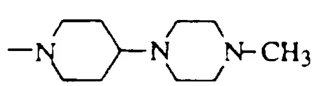
M.p. 228-230°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: 2HCl

Example 78

R^1 R^2 :  R^4: H m: 1

R^5 and A combine to form: 

R^{11b}: H R^{17}: 

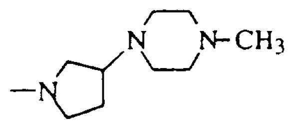
M.p. 203-205°C Crystalline form: White powder Form: 3HCl

Solvent for recrystallization: Methanol-diethyl ether

Table 58

Example 79

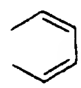
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

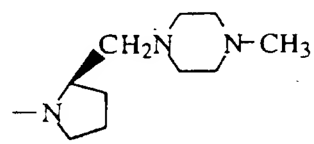
R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

M.p. 202-204°C Crystalline form: White powder

Solvent for recrystallization: Ethyl acetate-n-hexane Form: 3HCl

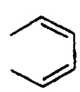
Example 80

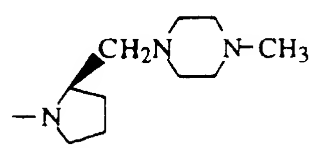
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

Crystalline form: Yellow powder Form: 2HCl NMR (9)

Example 81

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

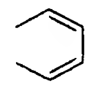
R^{11b}: H R^{17}:  R^5: Cl (2-position)

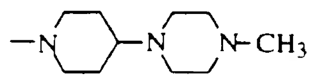
M.p. 171°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Table 59

Example 82

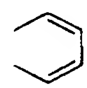
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 2

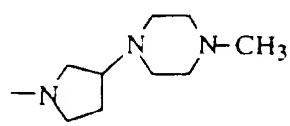
R^{11b}: H R^{17}:  R^5: CH_3 (2- and 6-positions)

M.p. 233-235°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: Free

Example 83

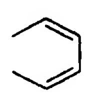
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 2

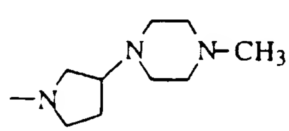
R^{11b}: H R^{17}:  R^5: CH_3 (2- and 6-positions)

M.p. 206-210°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: Free

Example 84

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

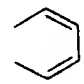
R^{11b}: H R^{17}:  R^5: F (2-position)

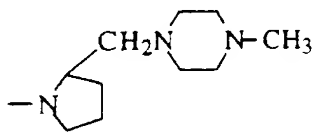
M.p. 205-208°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 60

Example 85

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: F (2-position)

M.p. 173-175°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

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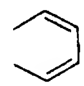
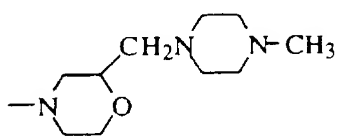
Example 86

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: $C_2H_5OOC(CH_2)_2-$ (2-position)

R^{11b}: H R^{17}: 

M.p. 152.4-156.3°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 3HCl

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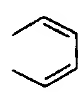
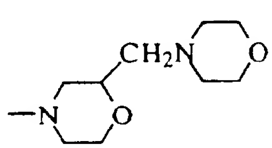
Example 87

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: F (2-position)

M.p. 150-153°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-diethyl ether Form: Free

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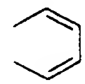
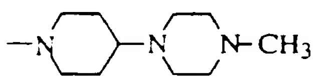
Table 61

Example 88

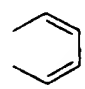
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

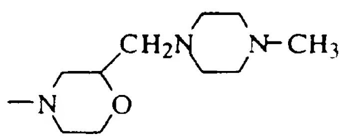
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water NMR (11)

Example 89

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 203-206°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl et her Form: 2HCl

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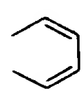
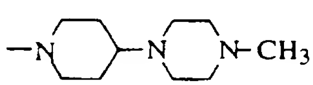
Example 90

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

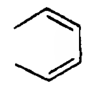
R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

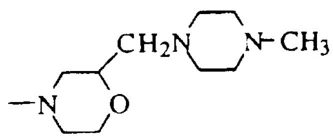
M.p. 161.7-165°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl et her Form: 3HCl

Table 62

Example 91

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

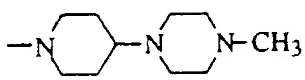
R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

M.p. 153-155.5°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl et her   Form: 3HCl

Example 92

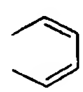
R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

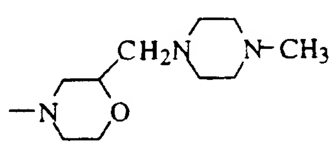
R^{11b}: H R^{17}:  R^5: CF_3 (2-position)

M.p. 185-187°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Isopropyl alcohol-water   Form: 2HCl

Example 93

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

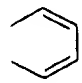
R^{11b}: H R^{17}:  R^5: CF_3 (2-position)

M.p. 175-178°C   Crystalline form: Pale yellow powder

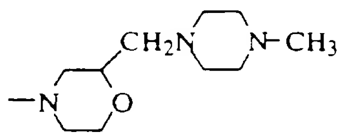
Solvent for recrystallization: Ethanol-water   Form: 2HCl

Table 63

Example 94

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: $CH_3COO(CH_2)_4-$ (2-position)

R^{11b}: H R^{17}: 

M.p. 151-154°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 3HCl

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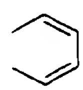
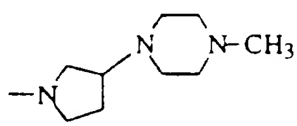
Example 95

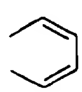
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

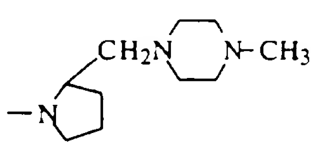
R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

M.p. 167-168°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Example 96

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

M.p. 135-137°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 3HCl

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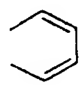
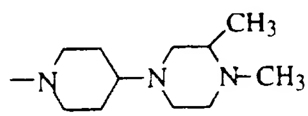
Table 64

Example 97

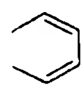
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

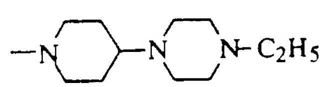
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 183.5-186°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 98

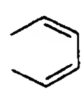
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

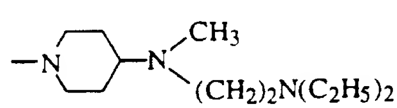
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 174-176°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 99

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

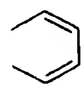
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

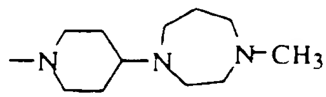
M.p. 153-154°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 65

Example 100

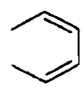
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

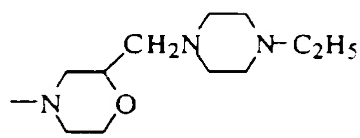
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 177.5-179.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Example 101

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 165-168°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl et her Form: 3HCl

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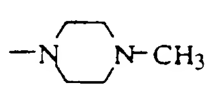
Example 102

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

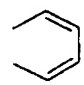
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 161.5-164°C Crystalline form: Yellow powder

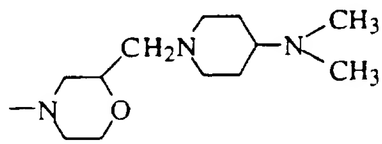
Solvent for recrystallization: Ethanol-water Form: HCl

Table 66

Example 103

R^1 R^2 : 

R^4: H A: $-CH_2-$ m: 1

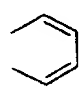
R^{11b}: H R^{17}: 

R^5: CH_3O (2-position)

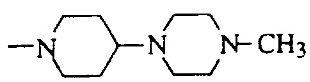
M.p. 181-183°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 104

R^1 R^2 : 

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

R^5: C_2H_5O- (2-position)

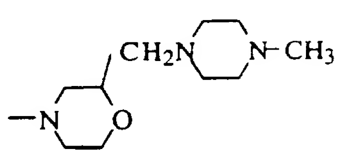
M.p. 174-177°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

Example 105

R^1 R^2 : 

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

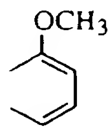
R^5: C_2H_5O- (2-position)

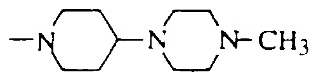
M.p. 194-196°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

Table 67

Example 106

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

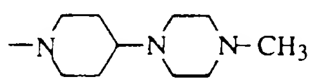
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 200-203°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 107

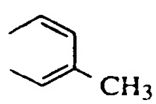
R^1 :  R^2 R^4: H A: $-CH(CH_3)-$ m: 1

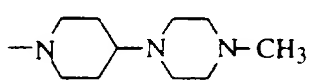
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 169-170°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: 2HCl

Example 108

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

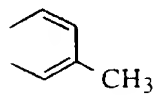
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

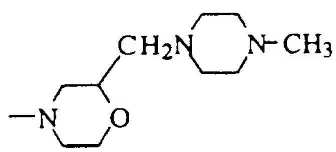
M.p. 181-189°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form [illegible]Cl NMR (12)

Table 68

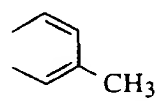
Example 109

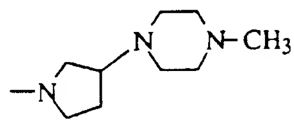
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 158-160°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 3HCl

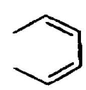
Example 110

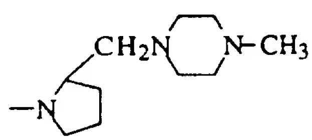
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 176.5-181.5°C Crystalline form: Yellow powder
Solvent for recrystallization: Ethanol-water Form: 3HCl NMR (13)

Example 111

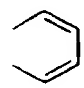
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

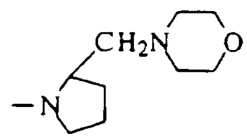
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 141-142°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 69

Example 112

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 131.5-133°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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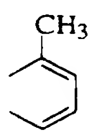
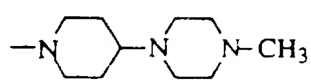
Example 113

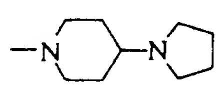
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

Crystalline form: Pale yellow amorphous Form: Free NMR (14)

Example 114

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

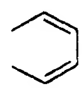
M.p. 140-142°C Form: Methanesulfonate

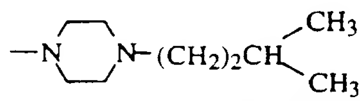
Solvent for recrystallization: Ethanol-diisopropyl ether

Crystalline form: Pale yellow powder

Table 70

Example 115

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 168.5-169°C   Crystalline form: White powder

Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

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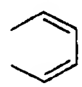
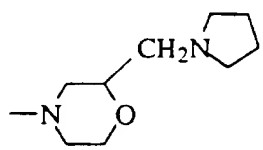
Example 116

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 128.2-131.5°C   Crystalline form: Yellow powder   Form: Free

Solvent for recrystallization: Ethanol-diethyl ether-dichloromethane

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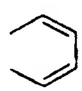
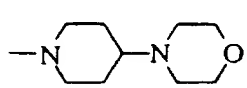
Example 117

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 144-146°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol   Form: Methanesulfonate

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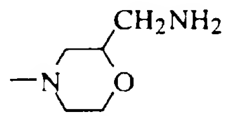
Table 71

Example 118

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

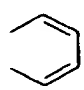
R^{11b}: H R^{17}:  R^5: C_2H_5O- (2-position)

M.p. 190-192°C   Crystalline form: Yellow powder

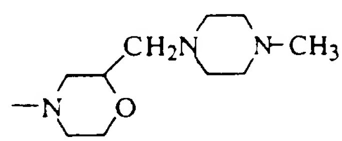
Form: Methanesulfonate

Solvent for recrystallization: Ethanol-isopropyl alcohol-diethyl ether-water

Example 119

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

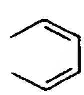
R^5: $CH_3OOC(CH_2)_2$- (2-position)

R^{11b}: H R^{17}: 

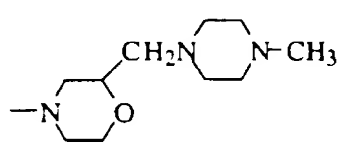
M.p. 110-111°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol   Form: Free

Example 120

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^5: $(CH_3)_2NOC(CH_2)_2$- (2-position)

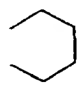
R^{11b}: H R^{17}: 

M.p. 162.5-164°C   Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water   Form: HCl

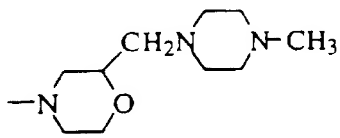
Table 72

Example 121

R^1 : 

R^2

R^4: H A: $-CH_2-$ m: 1

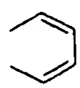
R^{11b}: H R^{17}: 

R^5: CH_3O (2-position)

M.p. 205-207.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

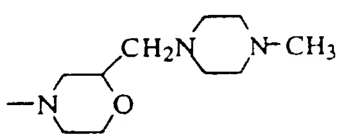
Example 122

R^1 : 

R^2

R^4: H A: $-CH_2-$ m: 1

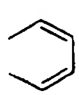
R^5: $(C_2H_5)_2NOCCH_2O$- (2-position)

R^{11b}: H R^{17}: 

M.p. 167-169°C Crystalline form: White powder

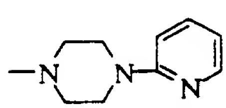
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 123

R^1 : 

R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

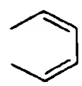
R^5: CH_3O- (2-position)

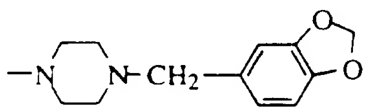
M.p. 190.5-192.5°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

Table 73

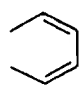
Example 124

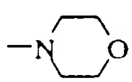
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{11b}: H R^{17}:  R^5: CH_3O- (2-position)

M.p. 148.2-149°C Crystalline form: Pale yellow powder Form: Free
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

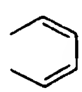
Example 125

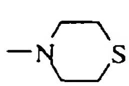
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{11b}: H R^{17}:  R^5: CH_3O- (2-position)

M.p. 211-211.5°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Example 126

R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

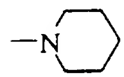
R^{11b}: H R^{17}:  R^5: CH_3O- (2-position)

M.p. 204-206°C Crystalline form: White needles
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 74

Example 127

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O- (2-position)

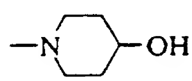
M.p. 168-170.4°C Crystalline form: White needles Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

---

Example 128

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O- (2-position)

M.p. 175.8-177.2°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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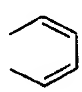
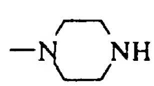
Example 129

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

M.p. 130-132.5°C Form: Dimethanesulfonate

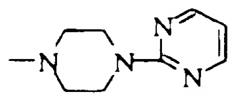
Solvent for recrystallization: Ethanol-diethyl ether

Crystalline form: Yellow powder

Table 75

Example 130

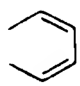
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

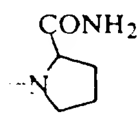
R^{11b}: H R^{17}:  R^5: C_2H_5O- (2-position)

M.p. 225-226°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-ethanol Form: Free

Example 131

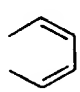
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

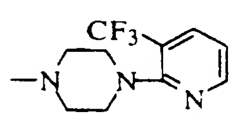
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 222-223°C Crystalline form: White powder

Solvent for recrystallization: Methanol-dichloromethane Form: Free

Example 132

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: C_2H_5O- (2-position)

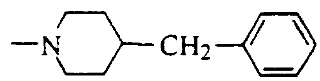
M.p. 122.5-125°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 76

Example 133

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

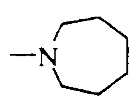
R^5: CH_3O (2-position)

M.p. 162-163°C   Crystalline form: White powder

Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

Example 134

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

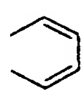
R^{11b}: H R^{17}: 

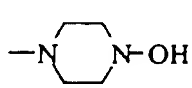
R^5: CH_3O (2-position)

M.p. 177.2-178°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

Example 135

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

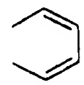
R^5: C_2H_5 (2-position)

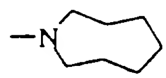
M.p. 140-155°C (decomp.)   Crystalline form: White powder   NMR (27)

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether   Form: Free

Table 77

Example 136

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 171-172.2°C Crystalline form: White needles Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

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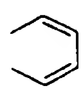
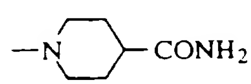
Example 137

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 232.5-233°C Crystalline form: Yellow powder

Solvent for recrystallization: Dichloromethane-ethanol Form: Free

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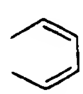
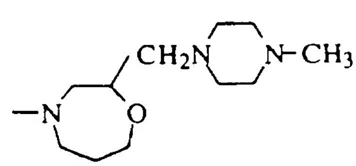
Example 138

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

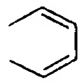
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

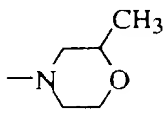
Crystalline form: Pale yellow amorphous NMR (28)

Form: 3HCl

Table 78

Example 139

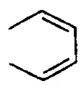
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

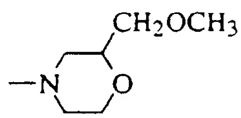
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 192-194°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Example 140

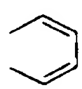
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

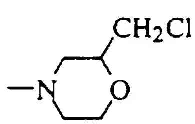
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 201-204 °C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Example 141

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

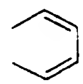
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 172-175°C Crystalline form: Yellow powder

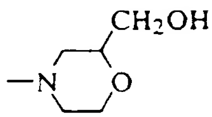
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 79

Example 142

R^1 :  R^2

R^{4}: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

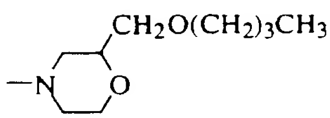
M.p. 146.5-148°C   Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

Example 143

R^1 :  R^2

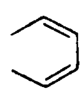
R^{4}: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

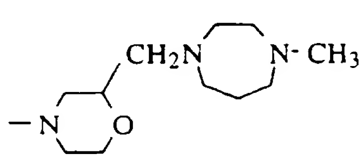
M.p. 114-117°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

Example 144

R^1 :  R^2

R^{4}: H   A: $-CH_2-$ m: 1

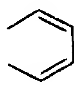
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

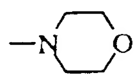
M.p. 176-181°C   Crystalline form: Pale yellow powder   Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether   NMR (29)

Table 80

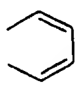
Example 145

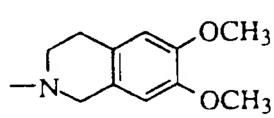
R^1
R^2 :  R^4: $-CH_2OCOC(CH_3)_3$ A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 106.5-108.2°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-diethyl ether-n-hexane Form: Free

Example 146

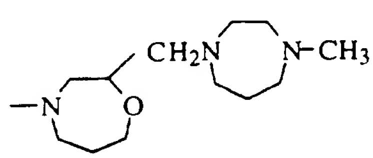
R^1
R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 189-190°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Example 147

R^1
R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

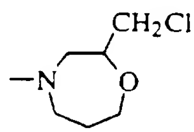
M.p. 151-153°C Crystalline form: White powder
Solvent for recrystallization: Ethyl acetate-diethyl ether Form: Free

Table 81

Example 148

R^1
: 
R^2

R^4: H   A: $-CH_2-$ m: 1

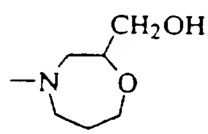
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 145-147°C   Crystalline form: White powder   Form: Free
Solvent for recrystallization: Ethyl acetate-chloroform

Example 149

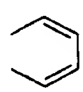
R^1
: 
R^2

R^4: H   A: $-CH_2-$ m: 1

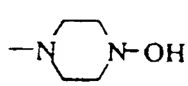
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 189-190.5°C   Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethyl acetate-chloroform   Form: Free

Example 150

R^1
: 
R^2

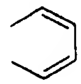
R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

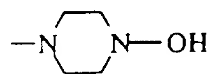
M.p. 196-199°C (decomp.)   Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-dichloromethane   Form: Free

Table 82

Example 151

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: C_2H_5O- (2-position)

M.p. 155-158°C (decomp.) Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

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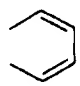
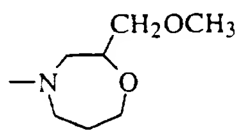
Example 152

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 162-164°C Crystalline form: White powder

Solvent for recrystallization: Ethyl acetate-diethyl ether Form: Free

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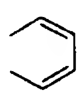
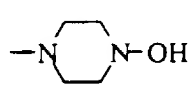
Example 153

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

M.p. 137-139°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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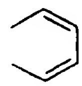
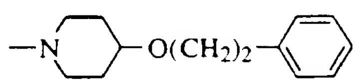
Table 83

Example 154

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 158-159°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

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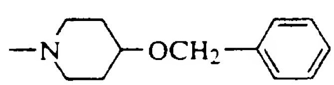
Example 155

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 154-154.5°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

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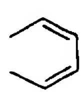
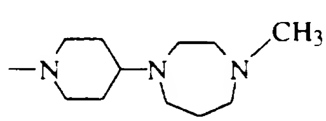
Example 156

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: $-CH_3$ R^{17}:  R^5: CH_3O (2-position)

M.p. 180-181.5°C Crystalline form: Dark yellow powder Form: HCl

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

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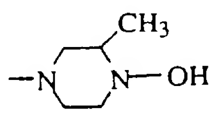
Table 84

Example 157

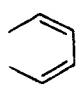
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

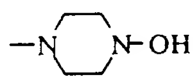
R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

M.p. 165-175°C (decomp.) Crystalline form: Yellow powder NMR (30)

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether Form: Free

Example 158

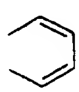
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

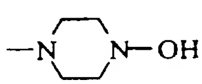
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 125-128°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 159

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

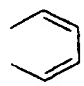
R^{11b}: H R^{17}:  R^5: CH_3 (2-position)

M.p. 195-195.5°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Table 85

Example 160

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

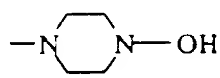
R^{11b}: H R^{17}:  R^5: CF_3 (2-position)

M.p. 188-190°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 161

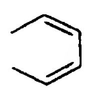
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

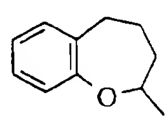
R^{11b}: H R^{17}:  R^5: F (2-position)

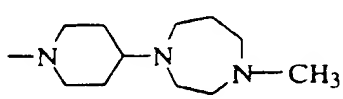
M.p. 197-200°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 162

R^1 R^2 :  R^4: H m: 1

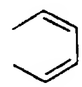
R^5 and A combine to form:  R^{11b}: H

R^{17}: 

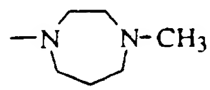
M.p. 138-141°C Crystalline form: White powder Form: Free

Table 86

Example 163

R^1 :  R^{4}: H A: $-CH_2-$ m: 1

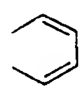
R^2

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

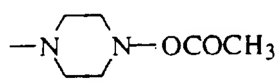
M.p. 155.5-158°C Crystalline form: Pale brown powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 164

R^1 :  R^{4}: H A: $-CH_2-$ m: 1

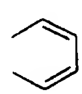
R^2

R^{11b}: H R^{17}:  R^5: CH_3 (2-position)

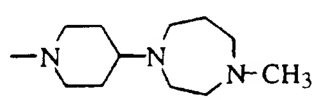
M.p. 163-166°C Crystalline form: Brown powder Form: Free

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

Example 165

R^1 :  R^{4}: H A: $-CH_2-$ m: 1

R^2

R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

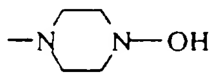
M.p. 161-163.4°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-dichloromethane-water

Table 87

Example 166

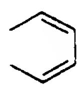
R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

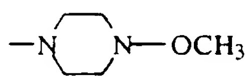
R^{11b}: H R^{17}:  R^5: n-Butyl (2-position)

M.p. 137-139°C   Crystalline form: Pale brown powder   Form: Free

Solvent for recrystallization: Ethanol-dichloromethane-water

Example 167

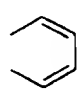
R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

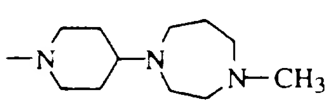
R^{11b}: H R^{17}:  R^5: CH_3 (2-position)

M.p. 215-217°C   Crystalline form: Pale yellow powder   Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 168

R^1 R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Heptyl (2-position)

M.p. 146.5-149°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-water   Form: 2HCl

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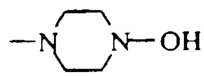
Table 88

Example 169

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Heptyl (2-position)

M.p. 152-153.5°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-dichloromethane-water Form: Free

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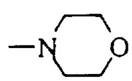
Example 170

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: n-Heptyl (2-position)

M.p. 166.5-169.3°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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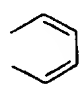
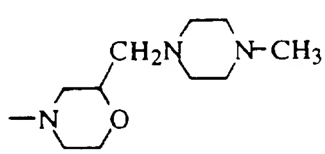
Example 171

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

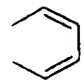
R^{11b}: H R^{17}:  R^5: n-Heptyl (2-position)

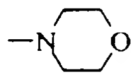
M.p. 155-165°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-dichloromethane-water NMR (31)

Table 89

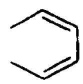
Example 172

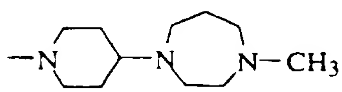
R^1 :  R^4: H A: $-(CH_2)_3-$ m: 1
R^2

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 219-220°C Crystalline form: Dark yellow powder Form: Free
Solvent for recrystallization: Ethanol-dichloromethane

Example 173

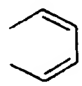
R^1 :  R^4: H A: $-(CH_2)_3-$ m: 1
R^2

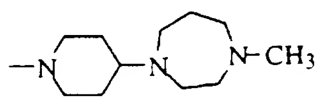
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 177-185°C Crystalline form: Dark yellow powder Form: 3HCl
Solvent for recrystallization: Ethanol-dichloromethane-water NMR (32)

Table 90

Example 175

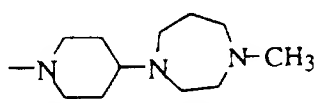
R^1
R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: C_2H_5O (2-position)

M.p. 182-184°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether

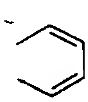
Example 176

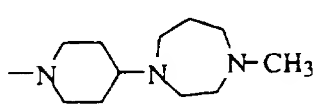
R^1
R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3 (2-position)

M.p. 265-270°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether NMR (33)

Example 177

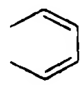
R^1
R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: Isopropyl (2-position)

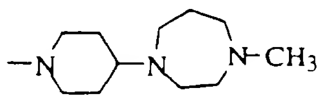
M.p. 203-207°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether

Table 91

Example 178

R^1 :  R^4: H A: $-CH_2-$ m: 2
R^2

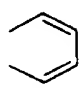
R^5: CH_3 (2- and 6-positions)

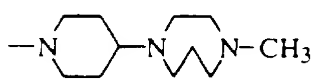
R^{11b}: H R^{17}: 

M.p. 234-238°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether

Example 179

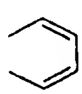
R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

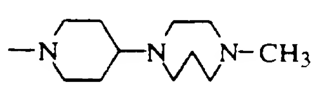
R^{11b}: H R^{17}:  R^5: F (2-position)

M.p. 214-217°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 180

R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

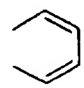
R^{11b}: H R^{17}:  R^5: C_2H_5 (2-position)

M.p. 188-190°C Crystalline form: Pale yellow powder Form: 2HCl

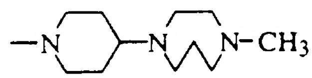
Solvent for recrystallization: Ethanol-water

Table 92

Example 181

R^1 :  R^4: H A: $-CH_2-$ m: 1

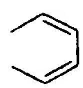
R^2

R^{11b}: H R^{17}:  R^5: n-Propyl (2-position)

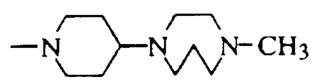
M.p. 164-167°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 182

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 165-168°C Crystalline form: Pale yellow powder Form: 2HCl

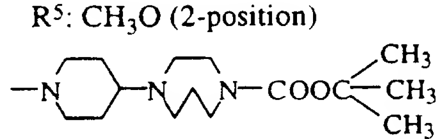
Solvent for recrystallization: Ethanol-water NMR (56)

Example 183

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^5: CH_3O (2-position)

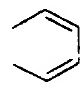
R^{11b}: H R^{17}: 

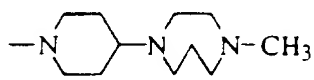
M.p. 143-145°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Table 93

Example 184

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: H

M.p. 215-218.5°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

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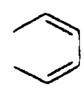
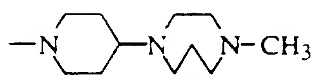
Example 185

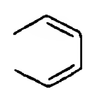
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CF_3 (2-position)

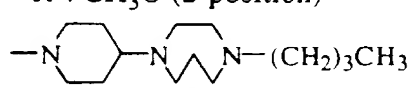
M.p. 101-106°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Diethyl ether-ethanol-water NMR (34)

Example 186

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: CH_3O (2-position)

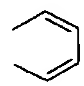
R^{11b}: H R^{17}: 

M.p. 179-183°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether

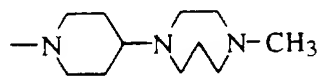
Table 94

Example 187

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

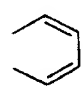
R^5: $C_2H_5CH(CH_3)-$ (2-position)

R^{11b}: H R^{17}: 

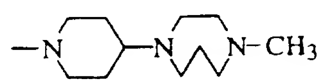
M.p. 129-131°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Isopropyl alcohol-water Form: Dioxalate

Example 188

R^1 :  R^4: H A: $-CH_2-$ m: 1

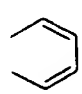
R^2

R^{11b}: H R^{17}:  R^5: C_2H_5 (3-position)

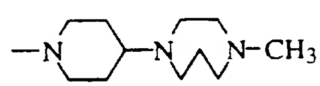
M.p. 163-165°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Water-ethanol-dichloromethane

Example 189

R^1 :  R^4: H A: $-CH_2-$ m: 1

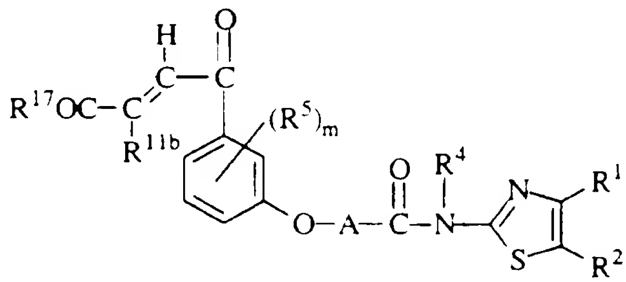
R^2

R^{11b}: H R^{17}:  R^5: $CH_3(CH_2)_4-$ (2-position)

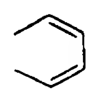
M.p. 161-162°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Isopropyl alcohol-water

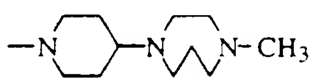
Table 95



Example 190

R^1 : 
R^2

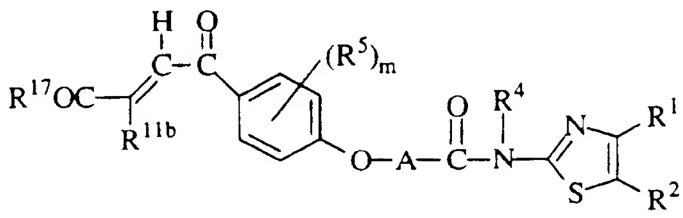
R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (4-position)

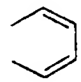
M.p. 166-168°C Crystalline form: Yellow powder Form: 2HCl

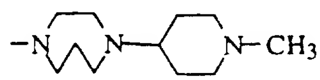
Solvent for recrystallization: Water-ethanol-dichloromethane

Table 96



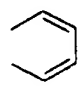
Example 191

R^1 and R^2:  R^4: H   A: $-CH_2-$ m: 1

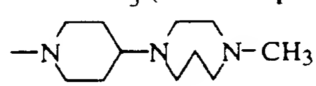
R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

M.p. 175-177°C   Crystalline form: White powder   Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether

Example 192

R^1 and R^2:  R^4: H   A: $-CH_2-$ m: 2

R^5: CH_3 (2- and 3-positions)

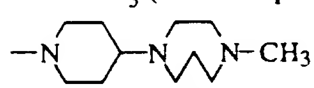
R^{11b}: H R^{17}: 

M.p. 158-162°C   Crystalline form: Pale yellow powder Form: Succinate
Solvent for recrystallization: Ethanol-diisopropyl ether

Example 193

R^1 and R^2:  R^4: H   A: $-CH_2-$ m: 2

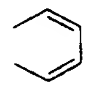
R^5: CH_3 (2- and 3-positions)

R^{11b}: H R^{17}: 

M.p. 126-128.5°C   Crystalline form: Yellow powder   Form: Succinate
Solvent for recrystallization: Ethanol-diethyl ether

Table 97

Example 194

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

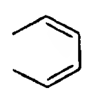
R^{11b}: H R^{17}: 

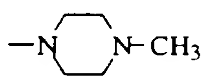
R^5: CF_3 (2-position)

M.p. 166-171°C Crystalline form: Pale yellow powder Form: HCl

Solvent for recrystallization: Isopropyl alcohol-ethanol NMR (35)

Example 195

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

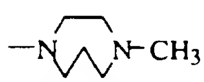
R^5: CH_3O (3-position)

M.p. 175-178°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Methanol

Example 196

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

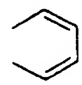
R^5: CH_3O (3-position)

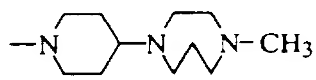
M.p. 240-245°C Crystalline form: Pale yellow powder Form: HCl

Solvent for recrystallization: Ethanol-water

Table 98

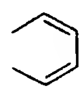
Example 197

R1 R2 :  R4: H A: $-CH_2-$ m: 1

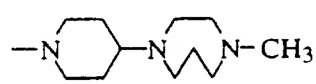
R11b: H R17:  R5: CH_3 (3-position)

M.p. 212-215°C Crystalline form: White powder Form: 2HCl
Solvent for recrystallization: Ethanol-water

Example 198

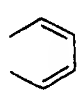
R1 R2 :  R4: H A: $-CH_2-$ m: 2

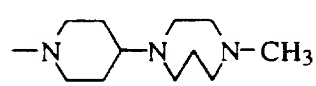
R5: $-(CH_2)_4-$ (combined at 2- and 3-positions)

R11b: H R17: 

M.p. 180-190°C Crystalline form: Yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-diethyl ether NMR (36)

Example 199

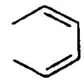
R1 R2 :  R4: H A: $-CH_2-$ m: 2

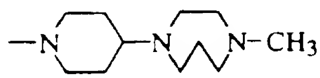
R11b: H R17:  R5: CH_3 (3- and 5-positions)

M.p. 210-216°C Crystalline form: White powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether NMR (37)

Table 99

Example 200

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

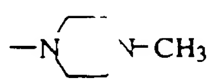
R^{11b}: H R^{17}:  R^5: Isopropyl (3-position)

M.p. 177.5-180.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 201

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 2

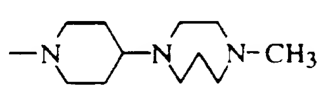
R^{11b}: H R^{17}:  R^5: CH_3 (3- and 5-positions)

M.p. 119-122.5°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-diisopropyl ether Form: Methanesulfonate

Example 202

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: $-COOCH_3$ (2-position)

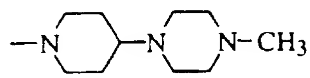
M.p. 169-172°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: Dimethanesulfonate

Table 100

Example 203

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

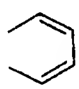
R^{11b}: H R^{17}: 

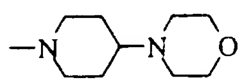
R^5: CH_3O (3-position)

M.p. 214-220°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Methanol

Example 204

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

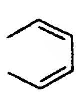
R^{11b}: H R^{17}: 

R^5: CH_3O (3-position)

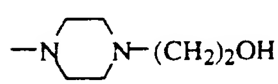
M.p. 195-197°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Dichloromethane-methanol

Example 205

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 2

R^5: $-(CH_2)_4-$ (combined at 2- and 3-positions)

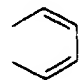
R^{11b}: H R^{17}: 

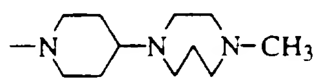
M.p. 151-153°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Water Form: Free

Table 101

Example 206

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

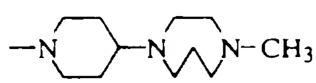
R^{11b}: H R^{17}:  R^5: n-Butyl (3-position)

M.p. 148-150.4°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Isopropyl alcohol-water-diethyl ether

Example 207

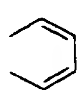
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

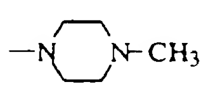
R^{11b}: H R^{17}:  R^5: $(CH_3)_3C-$ (2-position)

M.p. 142-144.5°C Crystalline form: Pale yellow powder Form: Oxalate

Solvent for recrystallization: Isopropyl alcohol-water

Example 208

R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

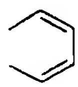
R^{11b}: H R^{17}:  R^5: CH_3 (3-position)

M.p. 139.2-140.8°C Crystalline form: Pale yellow powder

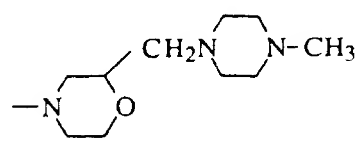
Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

Table 102

Example 209

R^1 :  R^{4}: H A: $-CH_2-$ m: 1

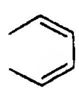
R^2

R^{11b}: H R^{17}:  R^5: CH_3O- (3-position)

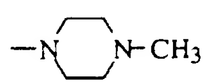
M.p. 158-163°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether NMR (38)

Example 210

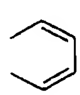
R^1 :  R^{4}: H A: $-CH_2-$ m: 1

R^2

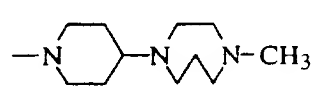
R^{11b}: H R^{17}:  R^5: n-Butyl (3-position)

M.p. 84-86°C Crystalline form: Yellow amorphous Form: Free

Example 211

R^1 :  R^{4}: H A: $-CH_2-$ m: 1

R^2

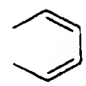
R^{11b}: H R^{17}:  R^5: n-Propyl (3-position)

M.p. 121-124°C Crystalline form: Pale yellow powder Form: Dioxalate

Solvent for recrystallization: Isopropyl alcohol-water

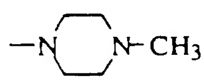
Table 103

Example 212

R^1
: 
R^2

R^4: H   A: $-CH_2-$ m: 2

R^5: CH_3 (2- and 3-positions)

R^{11b}: H R^{17}: 

M.p. 140-150°C   Crystalline form: Yellow powder   NMR (39)

Solvent for recrystallization: Acetone-water   Form: Methanesulfonate

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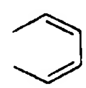
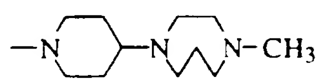
Example 213

R^1
: 
R^2

R^4: H   A: $-CH_2-$ m: 1

R^5: $-(CH_2)_2-CONH-$ (combined at 2- and 3-positions)

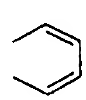
R^{11b}: H R^{17}: 

M.p. 173-175°C   Form: Dimethanesulfonate

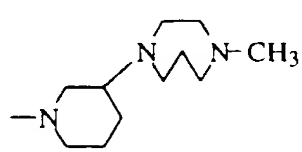
Solvent for recrystallization: Diethyl ether-ethanol-water

Crystalline form: Yellow powder

Example 214

R^1
: 
R^2

R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 168-172°C (decomp.)   Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-diethyl ether   Form: 2HCl

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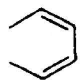
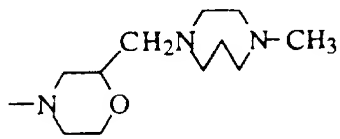
Table 104

Example 215

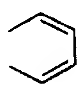
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

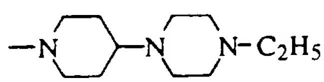
M.p. 155-160°C NMR (40)
Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

---

Example 216

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: CH_3O (3-position)

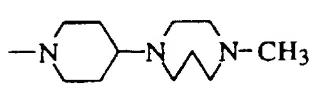
R^{11b}: H R^{17}: 

M.p. 163-165°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 217

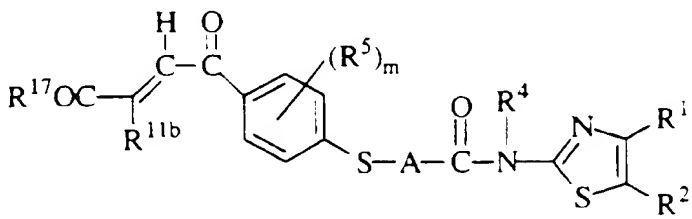
R^1: CH_3 R^4: H A: $-CH_2-$ m: 1

R^2: CH_3 R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

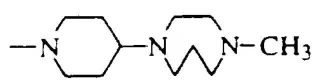
M.p. 190-193°C (decomp.) Crystalline form: Yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 105



Example 218

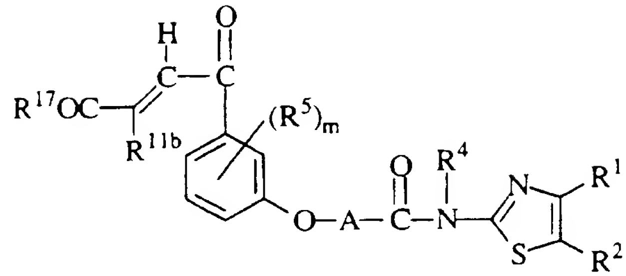
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (2-position)

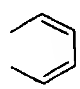
M.p. 174.4-176.5°C Crystalline form: Yellow powder

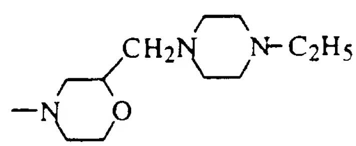
Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Table 106



Example 219

R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O- (3-position)

M.p. 162-165°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Diethyl ether-water-ethanol Form: 2HCl

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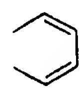
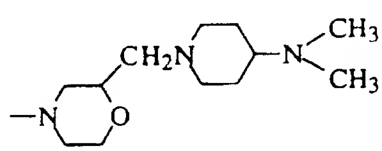
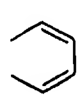
Example 220

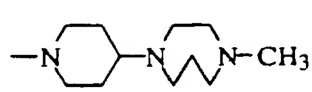
R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O- (3-position)

M.p. 206-211°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol
NMR (41)

Example 221

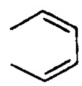
R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: $(CH_3)_2CHO-$ (3-position)

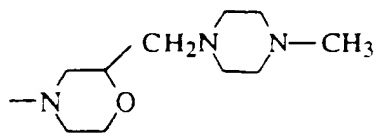
M.p. 168-172°C Crystalline form: Yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

Table 107

Example 222

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: $(CH_3)_2CHO-$ (3-position)

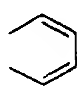
R^{11b}: H R^{17}: 

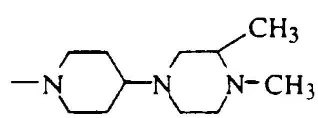
M.p. 203-208°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

NMR (42)

Example 223

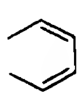
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

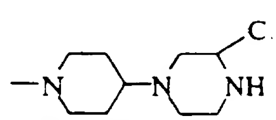
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 180-185°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Ethanol-water NMR (43)

Example 224

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

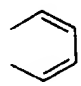
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 180-190°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol NMR (44)

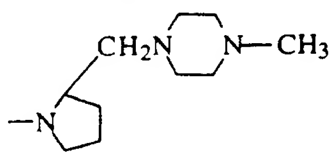
Table 108

Example 225

R^1
R^2 : 

R^4: H A: $-CH_2-$ m: 1

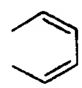
R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

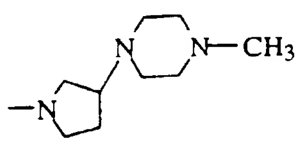
M.p. 157-160°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 226

R^1
R^2 : 

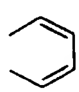
R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

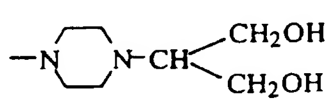
M.p. 171-174°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 227

R^1
R^2 : 

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 236-238°C Crystalline form: Pale yellow powder Form: HCl

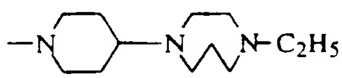
Solvent for recrystallization: Ethanol-water

Table 109

Example 228

R^1 :  R^4: H A: $-CH_2-$ m: 1

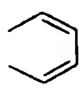
R^2

R^{11b}: H R^{17}: 

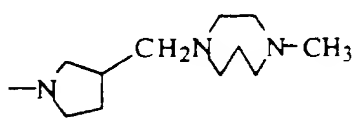
R^5: CH_3O (3-position)

M.p. 161-165°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

Example 229

R^1 :  R^4: H A: $-CH_2-$ m: 1

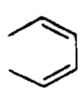
R^2

R^{11b}: H R^{17}: 

R^5: CH_3O (3-position)

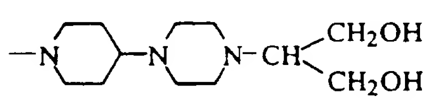
M.p. 191-194°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water

Example 230

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

M.p. 200-210°C (decomp.) Crystalline form: Yellow powder NMR (45)
Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

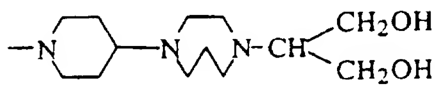
Table 110

Example 231

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^5: CH_3O (3-position)

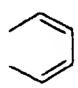
R^{11b}: H R^{17}: 

M.p. 165-170°C Crystalline form: Yellow powder Form: 2HCl

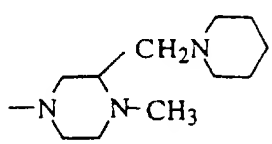
Solvent for recrystallization: Diethyl ether-ethanol-isopropyl alcohol-water

NMR (46)

Example 232

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

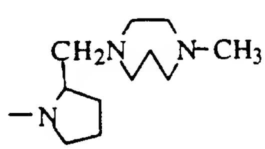
M.p. 150-170°C Crystalline form: Yellow powder NMR (47)

Solvent for recrystallization: Isopropyl alcohol Form: Dimethanesulfonate

Example 233

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

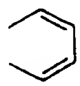
M.p. 166-169°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 111

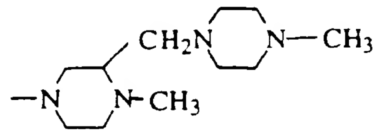
Example 234

R^1

: 

R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

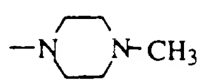
M.p. 186-200°C (decomp.) Crystalline form: Yellow powder Form: 3HCl

Solvent for recrystallization: Isopropyl alcohol NMR (48)

Example 235

R^1: CH_3 R^4: H A: $-CH_2-$ m: 1

R^2: CH_3 R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

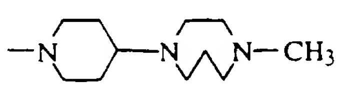
M.p. 204-210°C (decomp.) Crystalline form: Yellow powder Form: HCl

Solvent for recrystallization: Ethanol-water-diethyl ether NMR (49)

Example 236

R^1: H R^4: H A: $-CH_2-$ m: 1

R^2: H R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

M.p. 157-160°C Crystalline form: Yellow powder

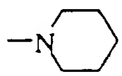
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 112

Example 237

R^1: H R^4: H   A: $-CH_2-$ m: 1

R^2: H R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

M.p. 83.1-85.5°C   Crystalline form: Yellow powder   Form: Free

Solvent for recrystallization: Ethanol-diethyl ether-n-hexane

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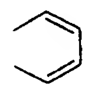
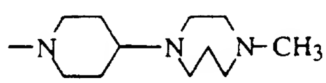
Example 238

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

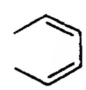
R^{11b}: H R^{17}:  R^5: F (3-position)

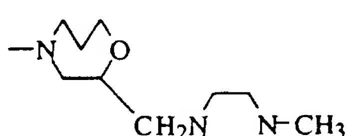
M.p. 215-220°C   Crystalline form: White powder   Form: 2HCl

Solvent for recrystallization: Ethanol-isopropyl alcohol-diethyl ether-water

NMR (50)

Example 239

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

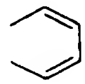
M.p. 149-154°C   Crystalline form: Pale yellow powder   Form: 2HCl

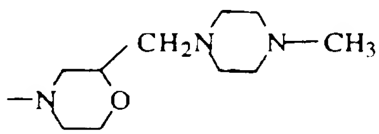
Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

NMR (51)

Table 113

Example 240

R^1 :  R^2 R^{4}: H   A: $-CH_2-$ m: 1

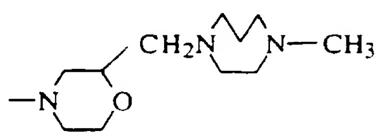
R^{11b}: H R^{17}:  R^5: Cl (3-position)

M.p. 126-129°C   Crystalline form: Pale yellow powder   Form: Free

Solvent for recrystallization: Ethanol-isopropyl alcohol

Example 241

R^1 :  R^2 R^{4}: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: $(CH_3)_3C$- (2-position)

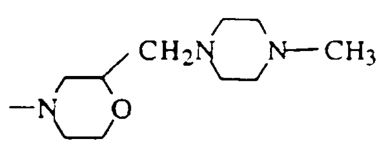
M.p. 181-183.8°C   Crystalline form: Pale yellow powder   Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether

Example 242

R^1: CH_3 R^{4}: H   A: $-CH_2-$ m: 1

R^2: CH_3 R^5: CH_3O (3-position)

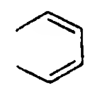
R^{11b}: H R^{17}: 

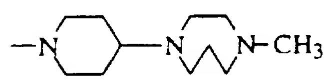
M.p. 192-197°C (decomp.)   Crystalline form: Yellow powder   Form: 2HCl

Solvent for recrystallization: Ethanol-water   NMR (52)

Table 114

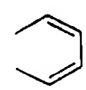
Example 243

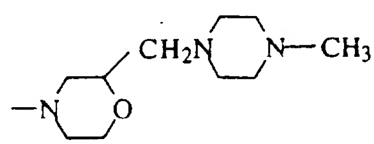
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: C_2H_5O (3-position)

M.p. 166-170°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water

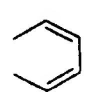
Example 244

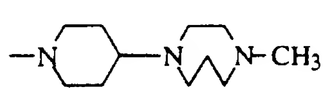
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CF_3CH_2O (3-position)

Crystalline form: Pale yellow powder Form: Dimethanesulfonate NMR (53)
Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

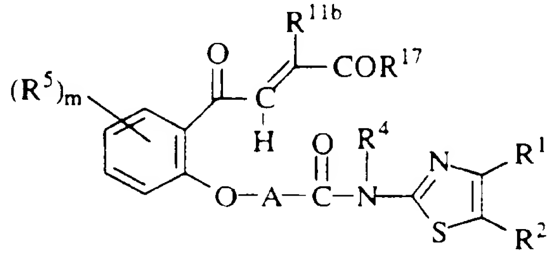
Example 245

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

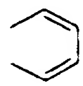
R^{11b}: H R^{17}:  R^5: CF_3CH_2O (3-position)

M.p. 179-183°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Isopropyl alcohol-ethanol-water-diethyl ether

Table 115

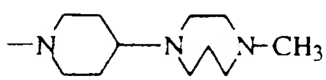


Example 246

R^1
: 
R^2

R^4: H A: $-CH_2-$ m: 2

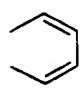
R^5: CH_3O (3- and 5-positions)

R^{11b}: H R^{17}: 

M.p. 182-185°C Crystalline form: Pale yellow powder

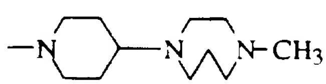
Solvent for recrystallization: Ethanol-water Form: 2HCl, trans-form

Example 247

R^1
: 
R^2

R^4: H A: $-CH_2-$ m: 2

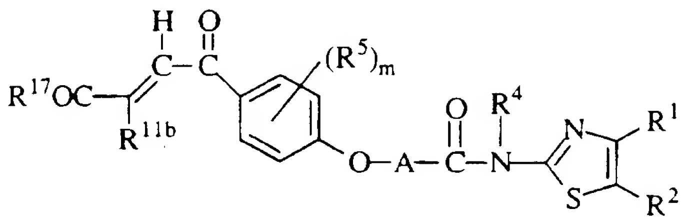
R^5: CH_3O (3- and 5-positions)

R^{11b}: H R^{17}: 

M.p. 177-183°C Crystalline form: Pale yellow powder

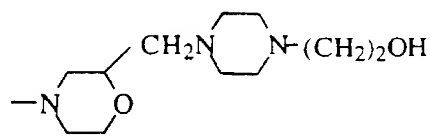
Solvent for recrystallization: Ethanol-water Form: 2HCl, cis-form

Table 116



Example 248

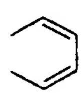
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

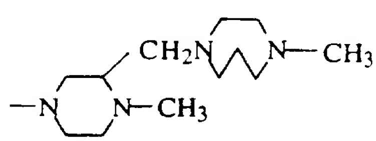
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 158-162°C Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether

Example 249

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

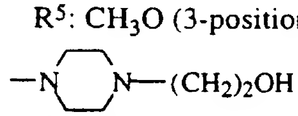
M.p. 167-171°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Example 250

R^1: CH_3 R^4: H A: $-CH_2-$ m: 1

R^2: CH_3 R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

M.p. 137-140°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

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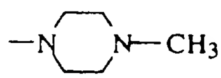
Table 117

Example 251

R^1: $(CH_3)_3C-$ (3-position) R^4: H A: $-CH_2-$ m: 1

R^2: H R^5: CH_3O (3-position)

R^{11b}: H R^{17}:



M.p. 129-131°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

Form: Dimethanesulfonate

Example 252

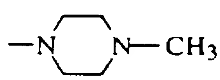
R^1

:

R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:



R^5: CH_3O (3-position)

M.p. 230-231°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: Dimethanesulfonate

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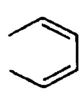
Example 253

R^1

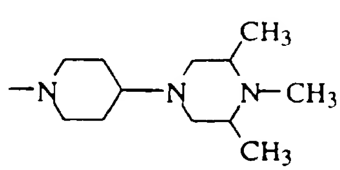
:



R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:



R^5: CH_3O (3-position)

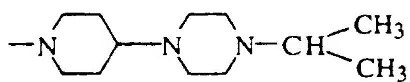
M.p. 159-164°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl NMR (54)

Table 118

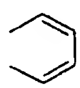
Example 254

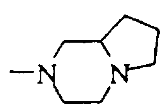
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 202-205°C (decomp.) Crystalline form: White powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

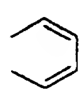
Example 255

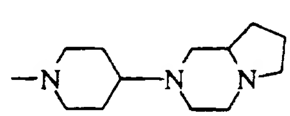
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 115-120°C Crystalline form: Pale brown powder NMR (55)
Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether
Form: Methanesulfonate

Example 256

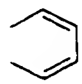
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

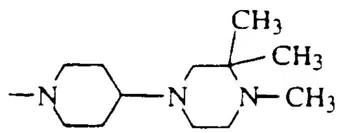
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 168.5-171.5°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 119

Example 257

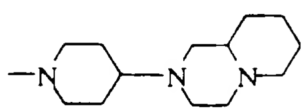
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 163-166°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

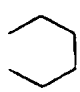
Example 258

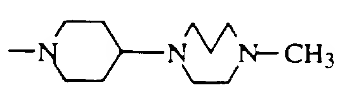
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 177.5-179°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 259

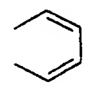
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

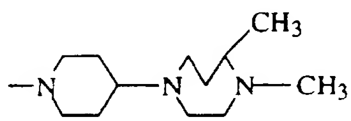
M.p. 165-168.5°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water-diethyl ether

Table 120

Example 260

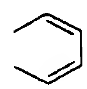
R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

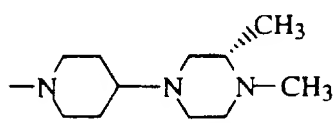
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 159-160°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 261

R^1 :  R^2

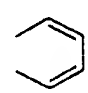
R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

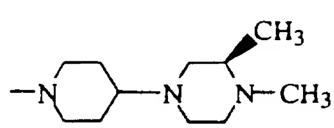
M.p. 177-178.2°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

S-(-)-compound: $[\alpha]_D^{22}$: -5.75° (c=2, water)

Example 262

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

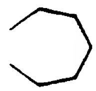
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 173-175°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

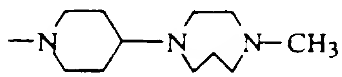
R-(+)-compound: $[\alpha]_D^{22}$: +4.35° (c=2, water)

Table 121

Example 263

R^1 : 
R^2

R^4: H A: $-CH_2-$ m: 1

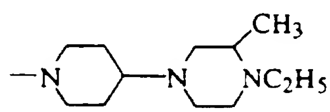
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 168-170.5°C Crystalline form: White powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 264

R^1 : 
R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

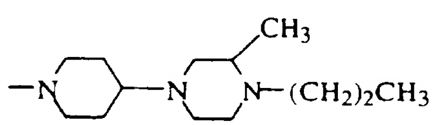
M.p. 156-159°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 265

R^1 : 
R^2

R^4: H A: $-CH_2-$ m: 1

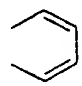
R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

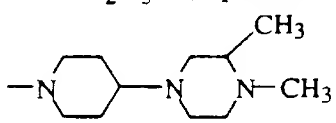
M.p. 176-179°C Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 122

Example 266

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

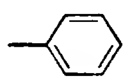
R^5: C_2H_5O (3-position)

R^{11b}: H R^{17}: 

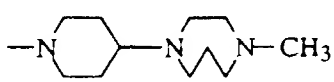
M.p. 159-161°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-isopropyl alcohol-diethyl ether

Example 267

R^1 :  R^4: H A: $-CH_2-$ m: 1

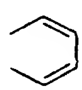
R^2: CH_3 R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

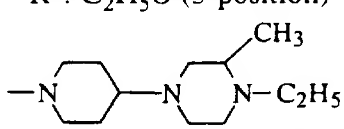
M.p. 166-169°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

Example 268

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^5: C_2H_5O (3-position)

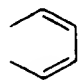
R^{11b}: H R^{17}: 

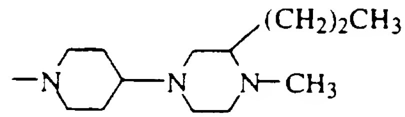
M.p. 215-217°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 123

Example 269

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

R^5: CH_3O (3-position)

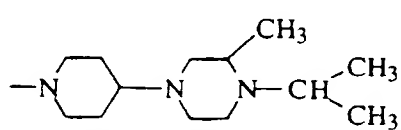
M.p. 174-177°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Ethanol-water

Example 270

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

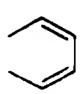
R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

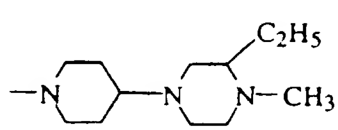
M.p. 202.5-205°C Crystalline form: White powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 271

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

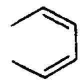
M.p. 155-158°C Crystalline form: Yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water-diisopropyl alcohol-diethyl ether

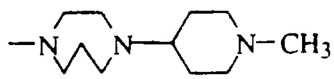
---

Table 124

Example 272

R^1 R^2 : 

R^4: H A: –CH_2– m: 1

R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 202-204°C Crystalline form: Pale yellow powder Form: 2HCl

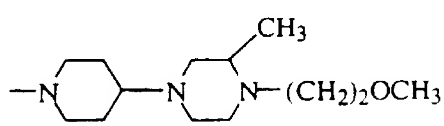
Solvent for recrystallization: Ethanol-water

Example 273

R^1 R^2 : 

R^4: H A: –CH_2– m: 1

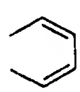
R^5: CH_3O (3-position)

R^{11b}: H R^{17}: 

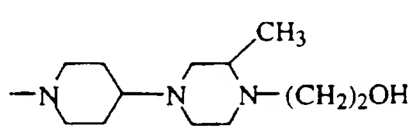
M.p. 163-165°C Crystalline form: Pale brown powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 274

R^1 R^2 : 

R^4: H A: –CH_2– m: 1

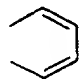
R^{11b}: H R^{17}:  R^5: CH_3O (3-position)

M.p. 160-162°C Crystalline form: Pale yellow powder

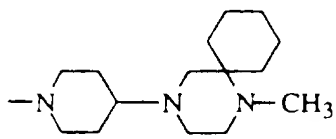
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 125

Example 275

R^1 : 
R^2

R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{17}: 

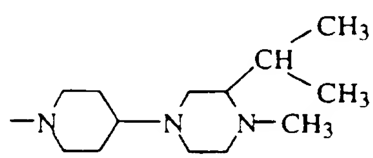
R^5: CH_3O (3-position)

M.p. 158-160°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-diethyl ether-water

Example 276

R^1 : 
R^2

R^4: H A: $-CH_2-$ m: 1

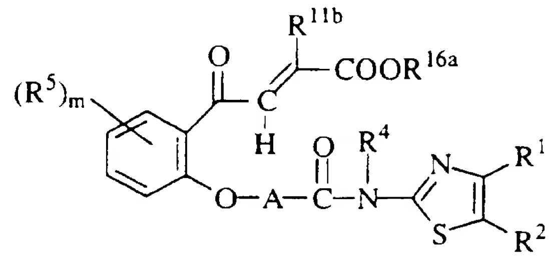
R^{11b}: H R^{17}: 

R^5: CH_3O (3-position)

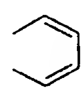
M.p. 164-166°C Crystalline form: Pale yellow powder Form: 2HCl
Solvent for recrystallization: Ethanol-water

Using the suitable starting compounds, the compounds as listed in Tables 126-128 are obtained in the same manner as in Example 5.

Table 126



Example 277

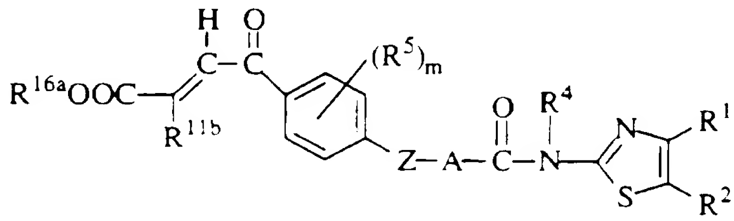
R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

R^{16a}: C_2H_5 R^{11b}: H R^5: H

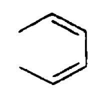
M.p. 130.5-132°C   Crystalline form: Pale orange powder   Form: Free

Solvent for recrystallization: Dimethylformamide-methanol

Table 127



Example 278

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{16a}: C_2H_5 Z: O

R^{11b}: H R^5: H

M.p. 183.5-184°C Crystalline form: White powder

Solvent for recrystallization: Dichloromethane-ethanol Form: Free

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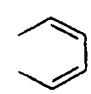
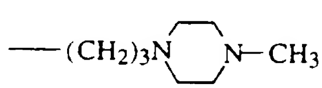
Example 279

R^1 :  R^2 R^{4}: H A: $-CH_2-$ m: 1

R^{16a}: C_2H_5 Z: O

R^{11b}: H R^5:  (2-position)

M.p. 221°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Diethyl ether-ethanol Form: 2HCl

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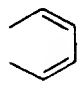
Table 128

Example 280

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

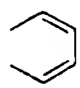
R^{16a}: CH_3 Z: O

R^{11b}: CH_3 R^5: CH_3O (2-position)

M.p. 124-126.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethyl acetate-n-hexane Form: Free

Example 281

R^1 :  R^2

R^4: H A: $-CH_2-$ m: 1

R^{16a}: C_2H_5 Z: S

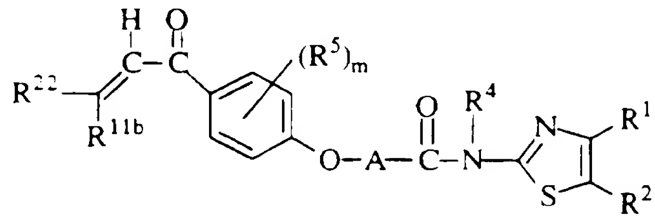
R^{11b}: H R^5: CH_3O (2-position)

M.p. 156-159°C Crystalline form: Yellow powder

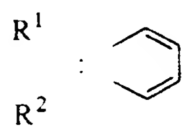
Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Using the suitable starting compounds, the compounds as listed in Tables 129-149 are obtained in the same manner as in Example 8.

Table 129

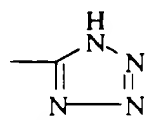


Example 282



R^4: H A: $-CH_2-$ m: 1

R^5: Isopropyl (2-position)

R^{11b}: H R^{22}: 

M.p. 137-138°C Crystalline form: Pale yellow powder Form: Free

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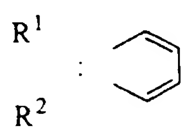
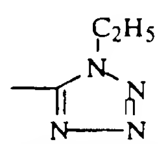
Example 283



R^4: H A: $-CH_2-$ m: 1

R^5: Isopropyl (2-position)

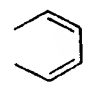
R^{11b}: H R^{22}: 

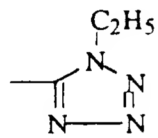
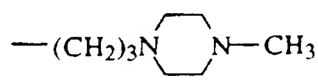
M.p. 197-198°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Dichloromethane-ethanol

Table 130

Example 284

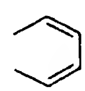
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

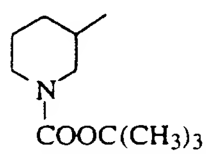
R^{11b}: H R^{22}:  R^5:  (2-position)

M.p. 240°C (decomp.) Crystalline form: Pale yellow powder Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 285

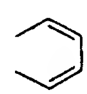
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

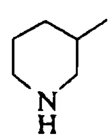
R^{11b}: H R^{22}:  R^5: Isopropyl (2-position)

M.p. 169.5-170°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol

Example 286

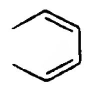
R^1 :  R^2 R^4: H A: $-CH_2-$ m: 1

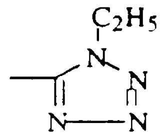
R^{11b}: H R^{22}:  R^5: Isopropyl (2-position)

Crystalline form: Pale brown powder Form: HCl NMR (7)

Table 131

Example 287

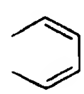
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

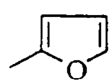
R^{11b}: H R^{22}:  R^5: $-(CH_2)_4OH$ (2-position)

M.p. 170.5-175.5°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethyl acetate-n-hexane NMR (8)

Example 288

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5: H

M.p. 201.5-202.5°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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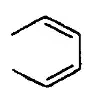
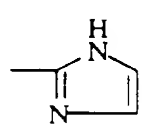
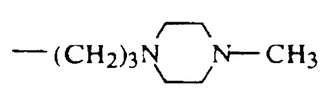
Example 289

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

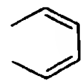
R^{11b}: H R^{22}:  R^5:  (2-position)

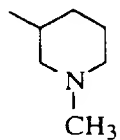
M.p. 195-198°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Table 132

Example 290

R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5: Isopropyl (2-position)

M.p. 101-103.5°C Crystalline form: Yellow amorphous Form: Free

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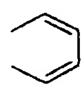
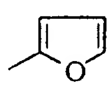
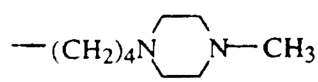
Example 291

R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

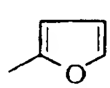
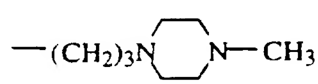
R^{11b}: H R^{22}:  R^5:  (2-position)

M.p. 148.2-153°C Crystalline form: Pale brown powder Form: 3HCl

Solvent for recrystallization: Ethanol-diethyl ether NMR (10)

Example 292

R^1, R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5:  (2-position)

M.p. 184-187°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

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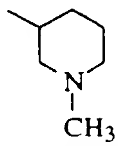
Table 133

Example 293

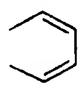
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

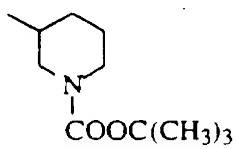
R^{11b}: H R^{22}:  R^5: F (2-position)

M.p. 151-154°C Crystalline form: White powder Form: HCl

Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

Example 294

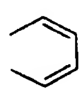
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

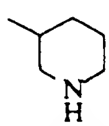
R^{11b}: H R^{22}:  R^5: Cl (2-position)

M.p. 207-209°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethyl acetate-n-hexane

Example 295

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

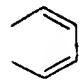
R^{11b}: H R^{22}:  R^5: Cl (2-position)

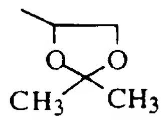
M.p. 164-166°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Methanol-diethyl ether Form: HCl

Table 134

Example 296

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

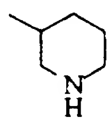
R^{11b}: H R^{22}:  R^5: F (2-position)

M.p. 141-141.5°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Dichloromethane-diethyl ether

Example 297

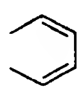
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

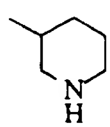
R^{11b}: H R^{22}:  R^5: CH_3O (2-position)

M.p. 186.5-191°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: Methanesulfonate

Example 298

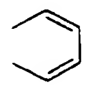
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

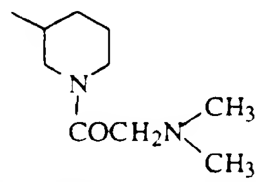
R^{11b}: H R^{22}:  R^5: CH_3 (2-position)

Crystalline form: Pale yellow amorphous Form: Free NMR (15)

Table 135

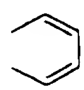
Example 299

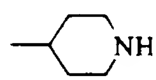
R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5: CH_3 (2-position)

Crystalline form: Pale yellow amorphous   Form: Free   NMR (16)

Example 300

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

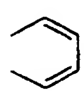
R^{11b}: H R^{22}:  R^5: C_2H_5O (2-position)

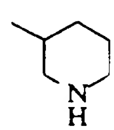
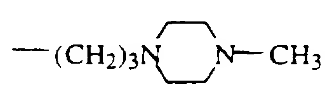
M.p. 202.5-203°C   Crystalline form: Pale powder

Solvent for recrystallization: Ethanol-isopropyl alcohol-water-diethyl ether

Form: Methanesulfonate

Example 301

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

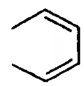
R^{11b}: H R^{22}:  R^5:  (2-position)

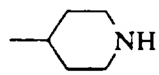
M.p. 186-189°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Water-ethanol-diethyl ether   Form: 3HCl

Table 136

Example 302

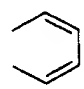
R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

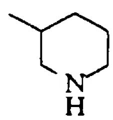
R^{11b}: H R^{22}:  R^5: CH_3O (3-position)

M.p. 135-145°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane NMR (17)

Example 303

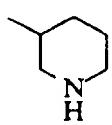
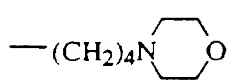
R^1 / R^2 :  R^4: H A: $\overset{C_2H_5}{\overset{|}{-CH-}}$ m: 1

R^{11b}: H R^{22}:  R^5: Cl (2-position)

Crystalline form: Pale yellow amorphous Form: Free NMR (18)

Example 304

R^1 / R^2 :  R^4: H A: $-CH_2-$ m: 1

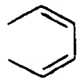
R^{11b}: H R^{22}:  R^5:  (2-position)

M.p. 146.5-150°C Crystalline form: White powder

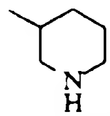
Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 137

Example 305

R^1 :  R^4: H A: $-CH_2-$ m: 2

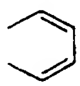
R^2

R^{11b}: H R^{22}:  R^5: CH_3O (2- and 6-positions)

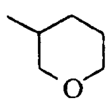
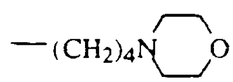
M.p. 115-120°C Crystalline form: Pale yellow powder NMR (19)

Solvent for recrystallization: Ethanol-diethyl ether Form: Methanesulfonate

Example 306

R^1 :  R^4: H A: $-CH_2-$ m: 1

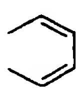
R^2

R^{11b}: H R^{22}:  R^5:  (2-position)

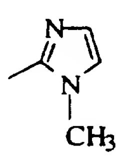
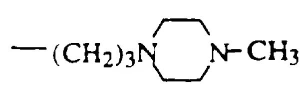
M.p. 207-208.5°C Crystalline form: White powder

Solvent for recrystallization: Diethyl ether-ethanol Form: Methanesulfonate

Example 307

R^1 :  R^4: H A: $-CH_2-$ m: 1

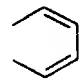
R^2

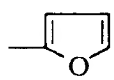
R^{11b}: H R^{22}:  R^5:  (2-position)

Crystalline form: Pale yellow amorphous Form: Free NMR (20)

Table 138

Example 308

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

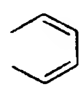
R^{11b}: H R^{22}:  R^5: 

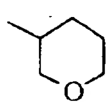
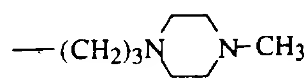
(2-position)

M.p. 139-141°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol Form: Methanesulfonate

Example 309

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

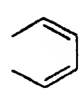
R^{11b}: H R^{22}:  R^5: 

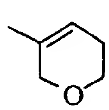
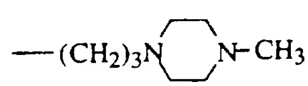
(2-position)

M.p. 194-197°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: Dimethanesulfonate

Example 310

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5: 

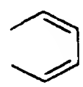
(2-position)

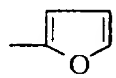
M.p. 218-220°C Crystalline form: Pale yellow powder

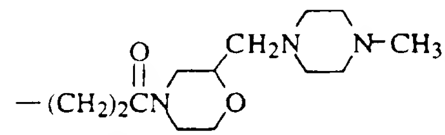
Solvent for recrystallization: Ethanol-water Form: Dimethanesulfonate

Table 139

Example 311

R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{22}: 

R^{11b}: H R^5: 

(2-position)

M.p. 182.5-186°C Crystalline form: Yellow powder

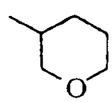
Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

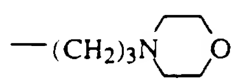
---

Example 312

R^1: CH_3 R^4: H A: $-CH_2-$ m: 1

R^2: CH_3

R^{11b}: H R^{22}: 

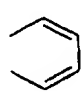
R^5: 

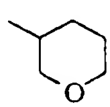
(2-position)

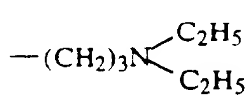
Crystalline form: White powder Form: Methanesulfonate

Solvent for recrystallization: Ethanol-diethyl ether NMR (21)

Example 313

R^1 :  R^4: H A: $-CH_2-$ m: 1
R^2

R^{11b}: H R^{22}: 

R^5: 

(2-position)

M.p. 140-141°C Crystalline form: White powder Form: Methanesulfonate

Solvent for recrystallization: Ethanol-isopropyl alcohol-diethyl ether

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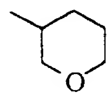
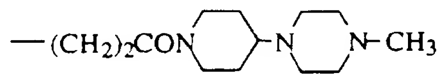
Table 140

Example 314

R^1 / R^2 : 

R^4: H   A: $-CH_2-$ m: 1

R^{22}: 

R^{11b}: H R^5:  (2-position)

M.p. 166-177°C   Crystalline form: White powder   NMR (22)

Solvent for recrystallization: Ethanol-diethyl ether   Form: 2HCl

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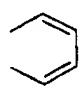
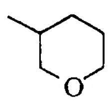
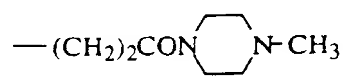
Example 315

R^1 / R^2 : 

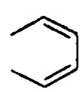
R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^{22}:  R^5:  (2-position)

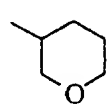
M.p. 156-157°C   Crystalline form: White powder

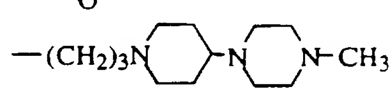
Solvent for recrystallization: Ethanol   Form: Free

Example 316

R^1 / R^2 : 

R^4: H   A: $-CH_2-$ m: 1

R^{22}: 

R^{11b}: H R^5:  (2-position)

M.p. 191-192°C   Crystalline form: White powder   Form: 3HCl

Solvent for recrystallization: Ethanol-water-isopropyl alcohol

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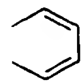
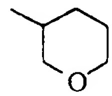
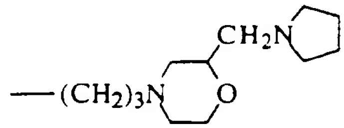
Table 141

Example 317

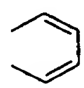
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

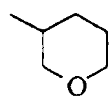
R^{22}: 

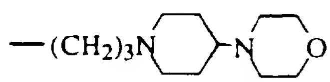
R^{11b}: H R^5:  (2-position)

Crystalline form: Pale yellow amorphous Form: Free NMR (23)

Example 318

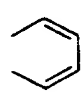
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

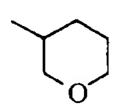
R^{22}: 

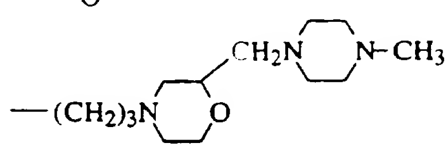
R^{11b}: H R^5:  (2-position)

Crystalline form: Colorless amorphous Form: Free NMR (24)

Example 319

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{22}: 

R^{11b}: H R^5:  (2-position)

M.p. 178-180°C Crystalline form: White powder Form: 3HCl

Solvent for recrystallization: Ethanol-isopropanol-diethyl ether-water

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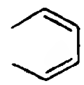
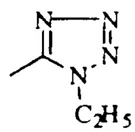
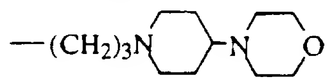
Table 142

Example 320

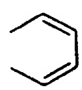
R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

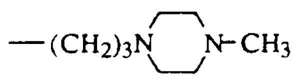
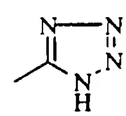
R^{22}: 

R^{11b}: H R^5:  (2-position)

Crystalline form: Pale yellow amorphous   Form: Free   NMR (25)

Example 321

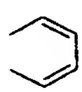
R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

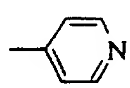
R^{11b}: H R^5:  (2-position) R^{22}: 

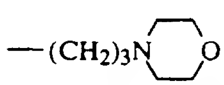
M.p. 198-201°C   Crystalline form: Pale yellow powder   Form: 2HCl

Solvent for recrystallization: Ethanol-water

Example 322

R^1 / R^2 :  R^4: H   A: $-CH_2-$ m: 1

R^{22}: 

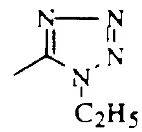
R^{11b}: H R^5:  (2-position)

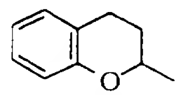
M.p. 177-178°C   Crystalline form: White powder   Form: Free

Solvent for recrystallization: Diethyl ether-ethanol-dichloromethane

Table 143

Example 323

R^1 : R^2 :  R^4: H m: 1 R^{22}: 

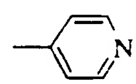
R^{11b}: H R^5 and A combine to form: 

M.p. 234-235°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethyl acetate-n-hexane

Example 324

R^1 : R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

M.p. 206-207°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

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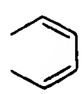
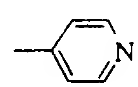
Example 325

R^1 : R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^5: n-Butyl (2-position) R^{22}: 

M.p. 195.5-196.5°C Crystalline form: Pale yellow needles

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

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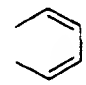
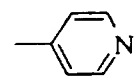
Table 144

Example 326

R^1 :  R^4: H A: $-CH_2-$ m: 1

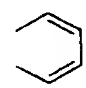
R^2

R^{11b}: H R^5: $-CH_2\underset{}{\overset{OCOCH_3}{\overset{|}{C}}}HCH_2OCOCH_3$ (2-position) R^{22}: 

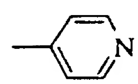
M.p. 134-136°C (decomp.) Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Dichloromethane-diisopropyl ether

Example 327

R^1 :  R^4: H A: $-CH_2-$ m: 1

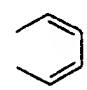
R^2

R^{11b}: H R^5: $-CH_2\overset{OH}{\overset{|}{C}}HCH_2OH$ (2-position) R^{22}: 

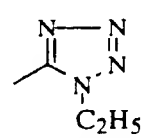
M.p. 207.6-214°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Dichloromethane NMR (26) Form: Free

Example 328

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

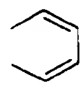
R^{11b}: H R^5: n-Butyl (2-position) R^{22}: 

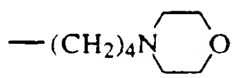
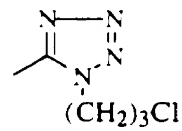
M.p. 191-193°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 145

Example 329

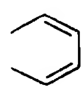
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

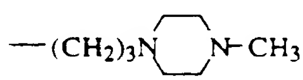
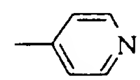
R^{11b}: H R^5:  (2-position) R^{22}: 

M.p. 112-114°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethyl acetate-diethyl ether

Example 330

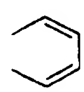
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

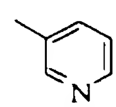
R^{11b}: H R^5:  (2-position) R^{22}: 

M.p. 209-211°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Example 331

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

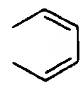
R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

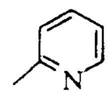
M.p. 208-210°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: Free

Table 146

Example 332

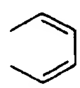
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

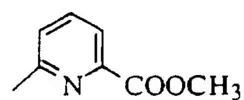
R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

M.p. 200-203°C Crystalline form: Yellow powder Form: Free

Solvent for recrystallization: Ethanol-isopropyl alcohol-dichloromethane

Example 333

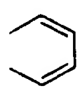
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

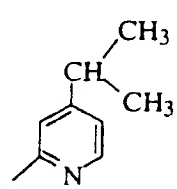
R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

M.p. 196-197°C Crystalline form: White powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 334

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

M.p. 203-204°C Crystalline form: White powder Form: Free

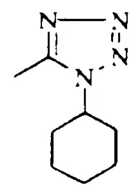
Solvent for recrystallization: Dichloromethane-ethanol-isopropyl alcohol

Table 147

Example 335

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

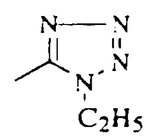
M.p. 206-208°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Dichloromethane-n-hexane

Example 336

R^1 :  R^4: H A: $-CH_2-$ m: 1

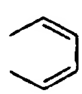
R^2

R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

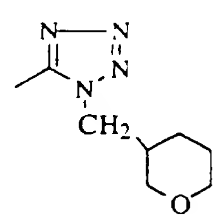
M.p. 190-192°C Crystalline form: Pale yellow needles Form: Free

Solvent for recrystallization: Chloroform-ethyl acetate

Example 337

R^1 :  R^4: H A: $-CH_2-$ m: 1

R^2

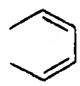
R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

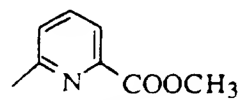
M.p. 207-209°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethyl acetate-diisopropyl ether

Table 148

Example 338

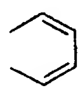
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

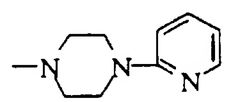
R^{11b}: H R^5: Isopropyl (2-position) R^{22}: 

M.p. 199.5-200.5°C Crystalline form: White powder

Solvent for recrystallization: Methanol-dimethylformamide Form: Free

Example 339

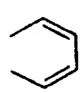
R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

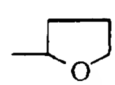
R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

M.p. 204-206°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethanol-dichloromethane

Example 340

R^1 R^2 :  R^4: H A: $-CH_2-$ m: 1

R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

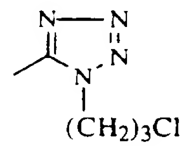
M.p. 115-117°C Crystalline form: Pale yellow powder Form: Free

Solvent for recrystallization: Ethyl acetate-diisopropyl ether

Table 149

Example 341

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

M.p. 225-227°C   Crystalline form: Pale yellow powder   Form: Free

Solvent for recrystallization: Ethyl acetate-diisopropyl ether

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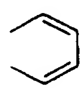
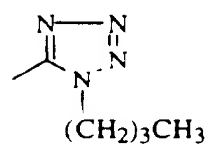
Example 342

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^5: C_2H_5O (2-position) R^{22}: 

M.p. 196.5-198°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Chloroform-ethyl acetate   Form: Free

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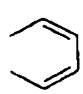
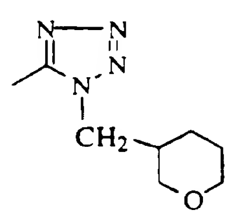
Example 343

R^1 :  R^2 R^4: H   A: $-CH_2-$ m: 1

R^{11b}: H R^5: CH_3O (2-position) R^{22}: 

M.p. 192-194°C   Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethyl acetate-diisopropyl ether   Form: Free

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^{1}H-NMR spectrum (NMR (1) to NMR (55)) as described in Tables 50-149 are as follows:

NMR (1) ($CDCl_3$) δppm: 2.33 (3H, s), 2.45 (4H, t, J=5Hz), 3.6-3.8 (4H, m), 4.85 (2H, s), 7.09 (2H, d, J=9Hz), 7.3-7.55 (2H, m), 7.50 (1H, d, J=15Hz), 7.8-7.95 (2H, m), 7.93 (1H, d, J=15Hz), 8.10 (2H, d, J=9Hz), 9.88 (1H, br)

NMR (2) (DMSO-d_6) δppm: 1.35-1.8 (2H, m), 2.0-2.3 (2H, m), 2.6-3.9 (11H, m), 2.81 (3H, s), 4.1-4.3 (1H, m), 4.5-4.7 (1H, m), 5.08 (2H, s), 7.15 (2H, d, J=9Hz), 7.3-7.55 (3H, m), 7.76 (1H, d, J=14Hz), 7.77 (1H, d, J=8.5Hz), 7.98 (1H, d, J=8Hz), 8.05 (2H, d, J=9Hz), 12.67 (1H, br)

NMR (3) (DMSO-d_6) δppm: 2.32 (3H, s), 2.45-4.50 (20H, m, 2.50 (s)), 5.14 (2H, s), 7.04 (1H, d, J=9.3Hz), 7.26-7.52 (3H, m), 7.70-8.10 (5H, m), 11.30-12.35, 12.35-13.20 (all 3H, br)

NMR (4) (DMSO-d_6) δppm: 2.60-4.50 (20H, m), 5.23 (2H, s), 7.20-7.55 (4H, m), 7.70-8.10 (5H, m), 11.30-13.20 (3H, br)

NMR (5) (DMSO-d_6) δppm: 0.926 (3H, t, J=7.4Hz), 1.5-1.9 (4H, m), 2.05-2.3 (2H, m), 2.6-2.8 (3H, m), 2.81 (3H, s), 3.0-3.3 (1H, m), 3.3-3.9 (9H, m), 4.15-4.35 (1H, m), 4.5-4.8 (1H, m), 5.12 (2H, s), 7.02 (1H, d, J=8.6Hz), 7.27-7.47 (3H, m), 7.74-7.99 (4H, m), 7.91 (1H, d, J=15Hz), 11.5-13.0 (3H, br)

NMR (6) (DMSO-d_6) δppm: 0.93 (3H, t, J=7.4Hz), 1.55-1.75 (2H, m), 2.6-2.8 (4H, m), 2.79 (3H, s), 3.0-4.15 (14H, m), 4.2-4.4 (1H, m), 5.12 (2H, s), 7.03 (1H, d, J=8.5Hz), 7.25-7.55 (2H, m), 7.45 (1H, s), 7.75-7.9 (4H, m), 7.79 (1H, d, J=8.5Hz)

NMR (7) (DMSO-d_6) δppm: 1.25 (6H, d, J=7Hz), 1.3-2.0 (4H, m), 2.6-3.5

(6H, m), 5.12 (2H, s), 6.77 (1H, dd, J=6Hz, J=15.5Hz), 7.00 (1H, d, J=8.5Hz), 7.17 (1H, d, J=15.5Hz), 7.25-7.5 (2H, m), 7.7-8.05 (4H, m), 9.14 (2H, br), 12.73 (1H, br)

NMR (8) ($CDCl_3$) δppm: 1.62 (3H, t, J=7.3Hz), 1.76-2.03 (4H, m), 2.85-3.09 (2H, m), 3.95-4.11 (2H, m), 4.52 (2H, q, J=7.3Hz), 4.88 (2H, s), 5.28 (1H, brs), 6.98 (1H, d, J=7.5Hz), 7.32-7.43 (1H, m), 7.43-7.55 (1H, m), 7.56 (1H, d, J=15.2Hz), 7.77-7.93 (2H, m), 8.00-8.12 (2H, m), 8.35 (1H, d, J=15.2Hz), 10.85 (1H, brs)

NMR (9) (DMSO-d_6) δppm: 0.93 (3H, t, J=7.4Hz), 1.5-1.8 (2H, m), 1.8-2.2 (4H, m), 2.69 (2H, t, J=7.4Hz), 2.8 (3H, s), 3.0-4.3 (12H, m), 4.3-4.6 (1H, m), 5.13 (2H, s), 7.03 (1H, d, J=8.6Hz), 7.17 (1H, d, J=15.1Hz), 7.30 (1H, t, J=7Hz), 7.74-7.99 (5H, m), 11.5-12.3 (1H, br), 12.3-13.3 (1H, br)

NMR (10) (DMSO-d_6) δppm: 1.56-1.91 (4H, m), 2.70-2.90 (7H, m), 3.10-3.52 (8H, m), 5.14 (2H, s), 6.65-6.75 (1H, m), 6.99-7.15 (2H, m), 7.28-7.40 (1H, m), 7.40-7.52 (1H, m), 7.52-7.60 (2H, m), 7.72-7.85 (1H, m), 7.90-8.08 (4H, m), 10.90-13.18 (3H, m)

NMR (11) (DMSO-d_6) δppm: 1.40-1.89 (2H, m), 1.96-2.32 (2H, m), 2.58-2.96 (4H, m), 2.96-3.83 (10H, m), 3.89 (3H, s), 4.06-4.34 (1H, m), 4.42-4.71 (1H, m), 5.08 (2H, s), 7.07 (1H, d, J=8.5Hz), 7.31 (1H, t, J=7.0Hz), 7.38-7.69 (3H, m), 7.69-7.92 (3H, m), 7.98 (1H, d, J=8.5Hz), 11.76 (2H, br), 12.71 (1H, br),

NMR (12) (DMSO-d_6) δppm: 1.40-1.85 (2H, m), 2.00-2.23 (2H, m), 2.40 (3H, s), 2.60-2.88 (1H, m), 2.81 (3H, s), 3.00-3.80 (10H, m), 3.89 (3H, s), 4.10-4.30 (1H, m), 4.48-4.78 (1H, m), 5.06 (2H, s), 7.04 (1H, d, J=8.5Hz), 7.21-7.31 (1H, m), 7.40 (1H, d, J=15.2Hz), 7.52-7.60 (1H, m), 7.60-7.88 (4H, m), 11.02-12.33 (2H, m), 12.33-12.80 (1H, m)

NMR (13) (DMSO-d_6) δppm: 2.40 (3H, s), 2.81 (3H, s), 2.90-4.35 (15H, m), 3.89 (3H, s), 5.07 (2H, s), 6.99-7.12 (1H, m), 7.12-7.35 (2H, m), 7.52-7.60 (1H, m), 7.60-7.91 (4H, m), 11.00-13.28 (3H, m)

NMR (14) ($CDCl_3$) δppm: 1.31-1.64 (2H, m), 1.77-2.07 (2H, m), 2.21-2.87 (10H, m), 2.29 (3H, s), 2.67 (3H, s), 3.06-3.26 (1H, m), 3.96-4.28 (1H, m), 4.10 (3H, s), 4.62-4.78 (1H, m), 4.87 (2H, s), 7.07 (1H, d, J=8.1Hz), 7.14-7.32 (2H, m), 7.52 (1H, d, J=14.9Hz), 7.61-7.77 (3H, m), 7.91 (1H, d, J=14.9Hz)

NMR (15) ($CDCl_3$) δppm: 1.20-2.16 (4H, m), 2.31-2.72 (3H, m), 2.44 (3H, s), 2.72-3.34 (2H, m), 4.85 (2H, s), 6.76-7.06 (3H, m), 7.21-7.58 (2H, m), 7.72-8.00 (4H, m)

NMR (16) ($CDCl_3$) δppm: 1.43-2.13 (4H, m), 2.28 (6H, s), 2.45 (3H, s), 2.53-3.28 (5H, m), 3.56-4.56 (2H, m), 4.86 (2H, s), 6.80-7.11 (3H, m), 7.28-7.53 (2H, m), 7.74-7.93 (4H, m)

NMR (17) ($CDCl_3$) δppm: 1.3-1.5 (2H, m), 1.7-1.9 (2H, m), 2.6-2.8 (2H, m), 2.8-3.3 (2H, m), 3.90 (3H, s), 4.80 (2H, s), 6.5-6.65 (2H, m), 6.73 (1H, d, J=15.5Hz), 6.87 (1H, dd, J=15.5Hz, J=6Hz), 7.3-7.55 (2H, m), 7.6-7.95 (4H, m)

NMR (18) ($CDCl_3$) δppm: 1.12 (3H, t, J=5.9Hz), 1.28-3.78 (11H, m), 4.97 (1H, t, J=5.3Hz), 6.68-7.53 (5H, m), 7.70-8.14 (4H, m)

NMR (19) (DMSO-d_6) δppm: 1.29-2.11 (4H, m), 2.32 (3H, s), 2.60-3.08 (3H, m), 3.08-3.56 (3H, m), 3.91 (6H, s), 4.85 (2H, s), 6.73-6.93 (1H, m), 7.19-7.54 (5H, m), 7.71-7.83 (1H, m), 7.93-8.05 (1H, m), 8.29-8.80 (1H, m), 12.14 (1H, brs)

NMR (20) ($CDCl_3$) δppm: 1.86-2.13 (2H, m), 2.39 (3H, s), 2.48-3.06 (12H, m), 3.82 (3H, s), 4.87 (2H, s), 6.82-8.09 (9H, m), 7.04 (1H, s), 7.21 (1H, s)

NMR (21) (DMSO-d_6) δppm: 1.4-2.2 (6H, m), 2.35 (3H, s), 2.65-2.85 (2H, m), 2.95-4.05 (14H, m), 5.07 (2H, s), 6.78 (1H, dd, J=7Hz, J=15.5Hz), 7.02 (1H, d, J=8.5Hz), 7.16 (1H, d, J=15.5Hz), 7.26 (1H, d, J=3.5Hz), 7.50 (1H, d, J=3.5Hz), 7.8-8.0 (2H, m), 9.58 (1H, br), 12.45 (1H, br)

NMR (22) (DMSO-d_6) δppm: 1.33-1.71 (5H, m), 1.80-2.00 (1H, m), 2.00-2.21 (2H, m), 2.65-2.77 (2H, m), 2.80 (3H, s), 2.88-3.10 (4H, m), 3.10-4.00 (14H, m), 4.00-4.23 (1H, m), 4.47-4.66 (1H, m), 5.13 (2H, s), 6.71-6.87 (1H, m), 6.98-7.09 (1H, m), 7.09-7.22 (1H, m), 7.26-7.40 (1H, m), 7.40-7.52 (1H, m), 7.72-7.83 (1H, m), 7.83-7.97 (2H, m), 7.97-8.08 (1H, m), 11.32-12.55 (2H, m), 12.70 (1H, brs)

NMR (23) ($CDCl_3$) δppm: 1.43-2.28 (12H, m), 2.28-3.01 (13H, m), 3.23-3.56 (2H, m), 3.56-4.09 (5H, m), 4.87 (2H, s), 6.74-7.02 (3H, m), 7.22-7.53 (2H, m), 7.70-7.97 (4H, m)

NMR (24) ($CDCl_3$) δppm: 1.43-2.18 (12H, m), 2.37-2.68 (8H, m), 2.86 (2H, t, J=7.7Hz), 2.97-3.16 (2H, m), 3.25-3.53 (2H, m), 3.56-3.80 (4H, m), 3.82-4.03 (2H, m), 4.85 (2H, s), 6.79-7.00 (3H, m), 7.22-7.53 (2H, m), 7.68-7.93 (4H, m)

NMR (25) ($CDCl_3$) δppm: 1.48-3.22 (19H, m), 1.62 (3H, t, J=7.4Hz), 3.57-3.78 (4H, m), 4.54 (2H, q, J=7.4Hz), 4.89 (2H, s), 6.99 (1H, d, J=8.5Hz), 7.22-7.53 (3H, m), 7.59 (1H, d, J=15.2Hz), 7.76-7.90 (2H, m), 7.92-8.09 (1H, m), 8.36 (1H, d, J=15.2Hz)

NMR (26) (DMSO-d_6) δppm: 2.65-2.8 (1H, m), 2.9-3.05 (1H, m), 3.3-3.45 (2H, m), 3.8 (1H, m), 4.65 (2H, br), 5.11 (2H, s), 7.06 (1H, d, J=8.5Hz), 7.25-7.5 (2H, m), 7.64 (1H, d, J=15.5Hz), 7.75-7.9 (3H, m), 7.95-8.2 (4H, m), 8.66 (2H, br), 12.58 (1H, br)

NMR (27) ($CDCl_3$) δppm: 1.36 (3H, t, J=7.5Hz), 2.6-3.6 (6H, m), 2.86 (2H,

q, J=7.5Hz), 4.05 (1H, m), 4.50 (1H, m), 4.87 (2H, s), 6.93 (1H, d, J=8Hz), 7.3-7.55 (3H, m), 7.8-8.0 (5H, m), 9.66 (1H, br)

NMR (28) (DMSO-d_6) δppm: 1.67-1.97 (2H, m), 2.80 (3H, s), 2.88-4.35 (17H, m), 3.90 (3H, s), 5.10 (2H, s), 7.08 (1H, d, J=8.6Hz), 7.20-7.66 (4H, m), 7.66-7.95 (3H, m), 7.99 (1H, d, J=7.1Hz), 12.70 (1H, s)

NMR (29) (DMSO-d_6) δppm: 2.05-2.35 (2H, m), 2.55-4.18 (22H, m), 4.18-4.42 (1H, m), 5.09 (2H, s), 7.07 (1H, d, J=8.6Hz), 7.27-7.57 (4H, m), 7.74-7.77 (3H, m), 7.98 (1H, d, J=7.1Hz), 11.52 (2H, br), 12.55 (1H, br)

NMR (30) ($CDCl_3$) δppm: 1.1-1.4 (3H, m), 1.37 (3H, t, J=7.5Hz), 2.5-2.8 (2H, m), 2.86 (2H, q, J=7.5Hz), 2.9-3.1 (1H, m), 3.2-3.6 (2H, m), 3.8-4.1 (1H, m), 4.5-4.8 (1H, m), 4.87 (2H, s), 5.35 (1H, br), 6.93 (1H, d, J=9Hz), 7.25-7.6 (3H, m), 7.75-8.05 (5H, m), 9.60 (1H, br)

NMR (31) (DMSO-d_6) δppm: 0.74-0.91 (3H, m), 1.12-1.44 (6H, m), 1.50-1.71 (2H, m), 2.55-2.90 (3H, m), 2.79 (3H, s), 2.90-3.80 (13H, m), 3.80-4.12 (4H, m), 4.19-4.42 (1H, m), 5.11 (2H, s), 7.01 (1H, d, J=8.7Hz), 7.27-7.51 (3H, m), 7.71-8.02 (5H, m), 11.00-13.00 (3H, m)

NMR (32) (DMSO-d_6) δppm: 1.45-1.89 (2H, m), 2.00-2.38 (6H, m), 2.55-2.86 (6H, m), 3.01-3.22 (1H, m), 3.22-3.94 (9H, m), 3.77 (3H, s), 3.99-4.50 (3H, m), 4.50-4.70 (1H, m), 7.07-7.20 (1H, m), 7.20-7.37 (1H, m), 7.37-7.54 (3H, m), 7.67-7.89 (3H, m), 7.89-8.03 (1H, m), 11.06-12.62 (3H, m)

NMR (33) (DMSO-d_6) δppm: 1.40-1.92 (2H, m), 1.92-2.30 (4H, m), 2.31 (3H, s), 2.55-2.90 (4H, m), 2.90-4.03 (10H, m), 4.03-4.34 (1H, m), 4.44-4.73 (1H, m), 5.11 (2H, s), 7.23 (1H, d, J=9.3H), 7.31 (1H, t, J=6.9Hz), 7.32-7.48 (2H, m), 7.74-7.86 (2H, m), 7.86-8.05 (3H, m), 10.88-12.00 (2H, m), 12.70 (1H, br)

NMR (34) (DMSO-d_6) δppm: 1.48-1.94 (2H, m), 2.00-2.39 (4H, m), 2.57-2.85 (4H, m), 2.85-4.03 (10H, m), 4.10-4.39 (1H, m), 4.48-4.71 (1H, m), 5.29 (2H, s), 7.21-7.57 (4H, m), 7.75-7.83 (2H, m), 7.98 (1H, d, J=7.4Hz), 8.23 (1H, s), 8.32 (1H, d, J=8.7Hz), 10.89-12.06 (2H, m), 12.76 (1H, br)

NMR (35) (DMSO-d_6) δppm: 2.88-3.28 (4H, m), 3.73-4.31 (4H, m), 5.30 (2H, s), 7.31 (1H, t, J=6.9Hz), 7.35-7.48 (3H, m), 7.75-7.85 (2H, m), 7.97 (1H, d, J=7.1Hz), 8.23 (1H, s), 8.33 (1H, d, J=8.7Hz), 9.37 (2H, br), 12.78 (1H, br)

NMR (36) (DMSO-d_6) δppm: 1.2-1.5 (2H, m), 1.6-1.85 (8H, m), 2.31 (3H, s), 2.5-3.15 (15H, m), 3.9-4.0 (1H,), 4.4-4.5 (1H, m), 5.04 (2H, s), 6.81 (1H, d, J=8.5Hz), 7.20 (1H, d, J=15.5Hz), 7.25-7.5 (3H, m), 7.55 (1H, d, J=8.5Hz), 7.75 (1H, d, J=7.5Hz), 7.97 (1H, d, J=7Hz)

NMR (37) (DMSO-d_6) δppm: 1.4-1.9 (2H, m), 2.12 (6H, s), 2.0-4.0 (19H, m), 4.45-4.6 (1H, m), 4.95 (2H, s), 6.77 (2H, s), 6.88 (1H, d, J=16Hz), 7.03 (1H, d, J=16Hz), 7.35-7.5 (2H, m), 7.76 (1H, d, J=7.5Hz), 7.99 (1H, d, J=8Hz), 11.24, 12.04 (all 1H, br), 11.74 (1H, br), 12.64 (1H, br)

NMR (38) (DMSO-d_6) δppm: 2.54-2.93 (5H, m), 2.93-3.78 (10H, m), 3.78-4.17 (7H, m), 4.17-4.44 (1H, m), 5.07 (2H, s), 6.65-6.78 (1H, m), 6.78-6.90 (1H, m), 7.18-7.71 (5H, m), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7.1Hz), 11.28 (2H, br), 12.68 (1H, br)

NMR (39) (DMSO-d_6) δppm: 2.22 (3H, s), 2.33 (3H, s), 2.36 (3H, s), 2.80 (3H, d, J=4Hz), 2.9-3.6 (6H, m), 4.15-4.3 (1H, m), 4.4-4.55 (1H, m), 5.06 (2H, s), 6.85 (1H, d, J=9Hz), 7.24 (1H, d, J=15.5Hz), 7.37 (1H, d, J=15.5Hz), 7.25-7.55 (3H, m), 7.76 (1H, d, J=7Hz), 7.98 (1H, d, J=7Hz), 9.76 (1H, br), 12.60 (1H, br)

NMR (40) (DMSO-d_6) δppm: 2.05-2.35 (2H, m), 2.54-2.98 (5H, m), 2.98-

3.85 (10H, m), 3.85-4.19 (7H, m), 4.19-4.47 (1H, m), 5.07 (2H, s), 6.65-6.79 (1H, m), 6.79-6.90 (1H, m), 7.18-7.71 (5H, m), 7.77 (1H, d, J=7.7Hz), 8.00 (1H, d, J=7.8Hz), 11.22 (2H, br), 12.68 (1H, br)

NMR (41) (DMSO-d_6) δppm: 1.89-2.44 (4H, m), 2.53-3.78 (16H, m), 3.78-4.13 (6H, m), 4.13-4.42 (1H, m), 5.07 (2H, s), 6.70 (1H, dd, J=2.2Hz, J=8.7Hz), 6.81 (1H, d, J=2.2Hz), 7.19-7.73 (5H, m), 7.76 (1H, d, J=7.8Hz), 7.98 (1H, d, J=7.0Hz), 10.61 (1H, br), 11.27 (1H, br), 12.71 (1H, br)

NMR (42) (DMSO-d_6) δppm: 1.30 (6H, d, J=5.9Hz), 2.55-4.19 (19H, m), 4.19-4.41 (1H, m), 4.82 (1H, sept, J=5.9Hz), 5.07 (2H, s), 6.60-6.71 (1H, m), 6.76-6.79 (1H, m), 7.22-7.49 (3H, m), 7.64 (1H, d, J=8.7Hz), 7.71-7.90 (2H, m), 7.98 (1H, d, J=7.1Hz), 11.81 (2H, br), 12.58 (1H, br)

NMR (43) (DMSO-d_6) δppm: 1.35 (3H, d, J=6Hz), 1.5-2.2 (4H, m), 2.5-3.8 (13H, m), 3.88 (3H, s), 4.1-4.3 (1H, m), 4.45-4.65 (1H, m), 5.06 (2H, s), 6.70 (1H, d, J=9Hz), 6.81 (1H, s), 7.27 (1H, d, J=15.5Hz), 7.25-7.5 (2H, m), 7.56 (1H, d, J=15.5Hz), 7.64 (1H, d, J=8.5Hz), 7.77 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 12.5-13 (3H, br)

NMR (44) (DMSO-d_6) δppm: 1.30 (3H, d, J=6.5Hz), 1.5-2.3 (4H, m), 2.55-2.8 (1H, m), 3.0-4.7 (13H, m), 3.88 (3H, s), 5.07 (2H, s), 6.70 (1H, d, J=9Hz), 6.81 (1H, m), 7.27 (1H, d, J=15.5Hz), 7.25-7.5 (2H, m), 7.56 (1H, d, J=15.5Hz), 7.64 (1H, d, J=8.5Hz), 7.77 (1H, d, J=8Hz), 7.98 (1H, d, J=7.5Hz), 9.85 (1H, br), 10.01 (1H, br), 12.25 (1H, br)

NMR (45) (DMSO-d_6) δppm: 2.05-2.20 (2H, m), 2.5-4.0 (18H, m), 3.88 (3H, s), 4.1-4.25 (1H, m), 4.5-4.65 (1H, m), 5.06 (2H, s), 6.70 (1H, d, J=8.5Hz), 6.81 (1H, m), 7.28 (1H, d, J=15Hz), 7.25-7.5 (2H, m), 7.56 (1H, d, J=15Hz), 7.64 (1H, d,

J=8.5Hz), 7.77 (1H, d, J=8Hz), 7.99 (1H, d, J=7.5Hz), 10.78 (1H, br), 11.94 (1H, br), 12.66 (1H, br)

NMR (46) (DMSO-d_6) δppm: 1.43-1.85 (2H, m), 1.97-2.42 (4H, m), 2.58-2.82 (1H, m), 2.82-4.08 (18H, m), 4.08-4.30 (1H, m), 4.42-4.72 (1H, m), 5.06 (2H, s), 5.22-5.68 (2H, m), 6.62-6.78 (1H, m), 6.78-6.95 (1H, m), 7.24-7.70 (5H, m), 7.77 (1H, d, J=6.2Hz), 7.99 (1H, d, J=5.8Hz), 10.35 (2H, br), 11.48 (1H, br)

NMR (47) (DMSO-d_6) δppm: 1.3-2.0 (6H, m), 2.37 (6H, s), 2.8-4.2 (16H, m), 3.88 (3H, s), 5.07 (2H, s), 6.71 (1H, dd, J=7H, J=2Hz), 6.81 (1H, d, J=2Hz), 7.25 (1H, d, J=15Hz), 7.25-7.5 (3H, m), 7.65-7.75 (2H, m), 7.77 (1H, d, J=7Hz), 7.98 (1H, d, J=6Hz), 9.40 (1H, br)

NMR (48) (DMSO-d_6) δppm: 2.4-4.5 (23H, m), 3.88 (3H, s), 5.09 (2H, s), 6.71 (1H, d, J=9Hz), 6.82 (1H, s), 7.2-7.75 (5H, m), 7.77 (1H, d, J=8Hz), 7.98 (1H, d, J=7Hz), 10.98 (1H, br), 11.58 (1H, br), 12.71 (1H, br)

NMR (49) (DMSO-d_6) δppm: 2.16 (3H, s), 2.23 (3H, s), 2.74 (3H, d, J=4Hz), 2.85-3.7 (6H, m), 3.86 (3H, s), 4.15-4.6 (2H, m), 4.95 (2H, s), 6.66 (1H, d, J=8.5Hz), 6.79 (1H, m), 7.27 (1H, d, J=15Hz), 7.61 (1H, d, J=15Hz), 7.63 (1H, d, J=8.5Hz), 11.42 (1H, br)

NMR (50) (DMSO-d_6) δppm: 1.39-1.90 (2H, m), 1.98-2.37 (4H, m), 2.58-2.90 (4H, m), 2.98-3.99 (10H, m), 4.11-4.32 (1H, m), 4.48-4.70 (1H, m), 5.09 (2H, s), 6.93-7.15 (2H, m), 7.20-7.62 (4H, m), 7.80-7.92 (2H, m), 7.99 (1H, d, J=7.3Hz), 10.80-11.95 (2H, m), 12.68 (1H, br)

NMR (51) (DMSO-d_6) δppm: 1.67-2.03 (2H, m), 2.80 (3H, s), 2.99-4.35 (20H, m), 5.07 (2H, s), 6.70 (1H, dd, J=2.2Hz, J=8.7Hz), 6.82 (1H, d, J=2.2Hz), 7.19-7.74 (5H, m), 7.77 (1H, d, J=7.5Hz), 7.99 (1H, d, J=7.9Hz). 10.80-12.32 (2H,

br), 12.69 (1H, br)

NMR (52) (DMSO-d_6) δppm: 2.15 (3H, s), 2.22 (3H, s), 2.83 (3H, s), 2.5-4.4 (17H, m), 3.86 (3H, s), 4.94 (2H, s), 6.65 (1H, d, J=8.5Hz), 6.78 (1H, s), 7.2-7.7 (3H, m), 12.05 (1H, br)

NMR (53) (DMSO-d_6) δppm: 2.36 (6H, s), 2.55-4.45 (20H, m), 4.92 (2H, q, J=8.9Hz), 5.08 (2H, s), 6.80 (1H, dd, J=2.3Hz, J=8.9Hz), 6.94 (1H, d, J=2.3Hz), 7.21-7.75 (5H, m), 7.77 (1H, d, J=8.1Hz), 7.98 (1H, d, J=7.1Hz), 9.95 (2H, br), 12.63 (1H, br)

NMR (54) (DMSO-d_6) δppm: 1.40 (6H, d, J=6.0Hz), 1.51-1.86 (2H, m), 2.05-2.30 (2H, m), 2.57-2.73 (1H, m), 2.79 (3H, s), 2.98-3.87 (8H, m), 3.88 (3H, s), 4.14-4.25 (1H, m), 4.40-4.70 (1H, m), 5.06 (2H, s), 6.70 (1H, dd, J=2.2Hz, J=8.8Hz), 6.81 (1H, d, J=2.2Hz), 7.23-7.66 (5H, m), 7.77 (1H, d, J=7.6Hz), 8.00 (1H, d, J=7.0Hz), 11.40-13.10 (3H, m)

NMR (55) (DMSO-d_6) δppm: 1.4-2.4 (4H, m), 2.34 (3H, s), 2.7-5.0 (9H, m), 3.88 (3H, s), 5.06 (2H, s), 6.71 (1H, dd, J=2Hz, J=9Hz), 6.82 (1H, d, J=2Hz), 7.2-7.5 (3H, m), 7.55-7.8 (3H, m), 7.99 (1H, d, J=7Hz), 9.6-10.2 (1H, m), 12.60 (1H, br)

NMR (56) (DMSO-d_6) δppm: 1.40-1.84 (2H, m), 2.00-2.42 (4H, m), 2.67 (1H, t, J=12.5Hz), 2.77 (3H, s), 3.12 (1H, t, J=12.5Hz), 3.24-4.05 (12H, m), 4.10-4.31 (1H, m), 4.48-4.71 (1H, m), 5.07 (2H, s), 6.70 (1H, dd, J=2.1Hz, J=8.7Hz), 6.82 (1H, d, J=2.1Hz), 7.19-7.62 (4H, m), 7.64 (1H, d, J=8.6Hz), 7.77 (1H, d, J=8.1Hz), 7.99 (1H, d, J=7.9Hz), 11.05-12.10 (2H, m), 12.68 (1H, br)

<u>Example 344</u>

2-{3-Allyloxy-4-[3-(1-piperidinyl)carbonylacryloyl]phenoxymethyl-carbonylamino}benzothiazole (0.55 g) is dissolved in methanol (70 ml) and

dioxane (40 ml), and thereto are added 10 % palladium-carbon (0.15 g), p-toluenesulfonic acid monohydrate (70 mg) and water (3 ml). The mixture is subjected to deaeration, and the mixture is refluxed under nitrogen atmosphere overnight. The mixture is filtered through a cerite pad, and to the filtrate is added water-methylene chloride, and the mixture is separated, and dried over sodium sulfate. The residue is crystallized from ethanol-methylene chloride, and recrystallized from dimethylformamide-ethanol to give 2-{3-hydroxy-4-[3-(1-piperidinyl)carbonylacryloyl]phenoxymethylcarbonylamino}benzothiazole (120 mg).

Yellow powder

M.p. 207.3-210°C

Example 345

To a solution of dimethyl [{2-methoxy-4-[2-(2-benzothiazolylamino-carbonyl)ethyl]benzoyl}methyl]phosphonate (6.4 g) in tetrahydrofuran (100 ml) is added 40 % glyoxylic acid (7.7 ml), and further thereto is added dropwise a 5 % aqueous sodium hydroxide solution (70 ml) under ice-cooling. The mixture is stirred for 30 minutes, and the mixture is acidified with 5 % hydro-chloric acid. The precipitated yellow powder is collected by filtration, washed with ethanol, dried, and then recrystallized from dimethylformamide-ethanol to give 2-{2-[3-methoxy-4-(trans-3-carboxyacryloyl)phenyl]ethylcarbonylamino}-benzothiazole (4.0 g).

Yellow powder

M.p. 260-261°C

Example 346

To tetrahydrofuran (50 ml) is added dimethyl [{2-dimethylamino-4-[(2-

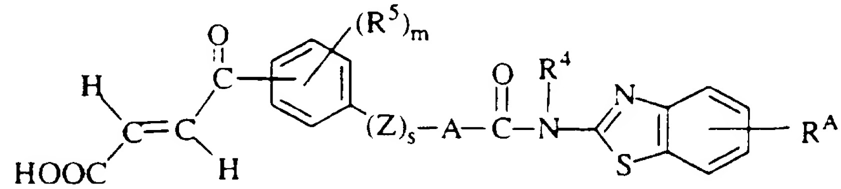
benzothiazolyl)aminocarbonylmethoxy]benzoyl}methyl]phosphonate (4.70 g), and thereto are added 5 % aqueous sodium hydroxide solution (40 ml) and glyoxylic acid (3.5 ml) under ice-cooling, and the mixture is stirred at the same temperature for 10 minutes. After confirming that the starting compounds are consumed, the mixture is acidified with hydrochloric acid, and concentrated under reduced pressure to remove the solvent. The precipitated crystals are collected by filtration, dissolved in dimethylformamide (100 ml), and the mixture is heated with stirring at 100°C for 30 minutes. After cooling, to the reaction solution is added isopropyl alcohol, and the precipitated crystals are collected by filtration. The crystals are recrystallized from dimethylformamide-isopropyl alcohol to give 1,1-dimethyl-2-carboxy-4-oxo-7-[(2-benzothiazolyl)-aminocarbonylmethoxy]-1,2,3,4-tetrahydroquinolinium chloride (2.46 g).

Pale green powder

M.p. 184.5-186.5°C

Using the suitable starting compounds, the compounds as listed in Table 150-160 are obtained in the same manner as in Example 1 or 5.

Table 150



Example 347

R^5: H A: $-CH_2CH_2-$ m: 1 s: 0

Z: - R^A: H R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 253.5-255°C Crystalline form: White powder

Solvent for recrystallization: Dimethylformamide-ethanol

Form: Free

Example 348

R^5: $-OCH_3$ (3-position) A: $-CH_2CH_2-$ m: 1 s: 0

Z: - R^A: H R^4: H

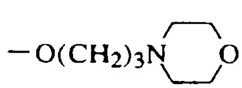
Position of $-COCH=CHCOOH$: 4-position

M.p. 260-261°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-ethanol

Form: Free

Example 349

R^5:  (5-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^A: H R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 184-186°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Dimethylformamide-ethanol-water

Form: HCl

Table 151

Example 350

R^5: $-OCH_3$ (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^A: $-N(CH_3)_2$ (6-position) R^4: H

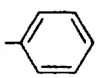
Position of $-COCH{=}CHCOOH$: 4-position

M.p. 263-264°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Dimethylformamide-ethanol-water

Form: Hydrate

Example 351

R^5: $-OCH_2-$  (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^A: H R^4: H

Position of $-COCH{=}CHCOOH$: 4-position

M.p. 294-297°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide

Form: Free

Example 352

R^5: $-OCH_2CH{=}CH_2$ (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^A: H R^4: H

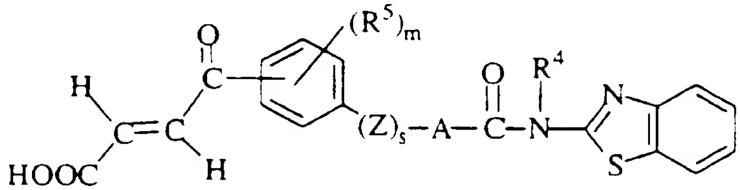
Position of $-COCH{=}CHCOOH$: 4-position

M.p. 248-254°C Crystalline form: Pale yellow powder

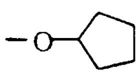
Solvent for recrystallization: Diluted hydrochloric acid

NMR (36) Form: Free

Table 152



Example 353

R^5:  (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^4: H

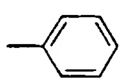
Position of –COCH=CHCOOH: 4-position

M.p. 270.0-271.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Example 354

R^5:  (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^4: H

Position of –COCH=CHCOOH: 4-position

M.p. 270.5-273.3°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Example 355

R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of –COCH=CHCOOH: 4-position

M.p. 203-206°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-dichloromethane

Form: Free

Table 153

Example 356

R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

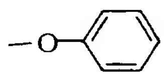
Position of $-COCH=CHCOOH$: 4-position

M.p. 232-234°C Crystalline form: Yellow powder

Solvent for recrystallization: Tetrahydrofuran-water

Form: Free

Example 357

R^5:  (3-position) A: $-CH_2-$ m: 1 s: 1

Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 237-245°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Tetrahydrofuran-water

NMR (37) Form: Free

Example 358

R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 127-138°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile

NMR (38) Form: Free

Table 154

Example 359

R^5: $-OCH_3$ (2- & 6-positions)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of –COCH=CHCOOH: 4-position

M.p. 137-138°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-ethanol-diethyl ether-n-hexane

Form: Free

Example 360

R^5: $-OCH_3$ (2- & 3-positions)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of –COCH=CHCOOH: 4-position

M.p. 235-237°C Crystalline form: Yellow powder

Solvent for recrystallization: Dichloromethane-dimethylformamide

Form: Free

Example 361

R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of –COCH=CHCOOH: 4-position

Crystalline form: Pale yellow powder NMR (39) Form: Free

Example 362

R^5: $-CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of –COCH=CHCOOH: 6-position

Crystalline form: Pale brown powder NMR (40) Form: Free

Table 155

Example 363

R^5: $-(CH_2)_3CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

Crystalline form: Yellow powder NMR (41) Form: Free

Example 364

R^5: $-SCH_3$ (3-position)

A: $-CH_2-$ m: 1 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

Crystalline form: Yellow powder NMR (42) Form: Free

Example 365

R^5: $-CH_2CH_3$ (2-position) & $-OCH_3$ (3-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

Crystalline form: Pale brown powder NMR (43) Form: Free

Example 366

R^5: $-OCH_3$ (3-position)

A: $-CH(CH_3)-$ m: 1 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

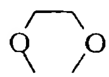
M.p. 225-228°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Dimethylformamide-ethanol-diethyl ether-water

Form: Free

Table 156

Example 367

R^5:  (2- & 3-positions)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 255-256°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Example 368

R^5: $-OCH_3$ (3-position)

A: $-(CH_2)_3-$ m: 1 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 239-241°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Example 369

R^5: $-(CH_2)_2CH_3$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 222-224°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Example 370

R^5: $-CH_2CH=CH_2$ (2-position) & $-OCH_3$ (5-position)

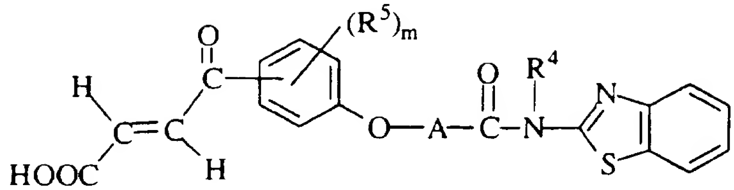
A: $-CH_2-$ m: 2 s: 1 Z: O R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 224-225°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Table 157



Example 371

R^5: $-OCH_3$ (2- & 5-positions)

A: $-CH_2-$ m: 2 R^4: H

Position of –COCH=CHCOOH: 4-position

NMR (44) Crystalline form: Yellow powder Form: Free

Example 372

R^5: $-CH_3$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 R^4: H

Position of –COCH=CHCOOH: 4-position

NMR (45) Crystalline form: Yellow powder

Example 373

R^5: $-OC_2H_5$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 R^4: H

Position of –COCH=CHCOOH: 4-position

M.p. 202-204°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Table 158

Example 374

R^5: $-Br$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 R^4: H

Position of $-COCH=CHCOOH$: 4-position

M.p. 238-239°C (decomp.) Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-acetonitrile Form: Free

Example 375

R^5: $-CH(CH_3)_2$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 R^4: H

Position of $-COCH=CHCOOH$: 4-position

NMR (46) Crystalline form: Yellow powder Form: Free

Example 376

R^5: $-(CH_2)_5CH_3$ (2-position) & $-OCH_3$ (5-position)

A: $-CH_2-$ m: 2 R^4: H

Position of $-COCH=CHCOOH$: 4-position

NMR (47) Crystalline form: Yellow powder Form: Free

Example 377

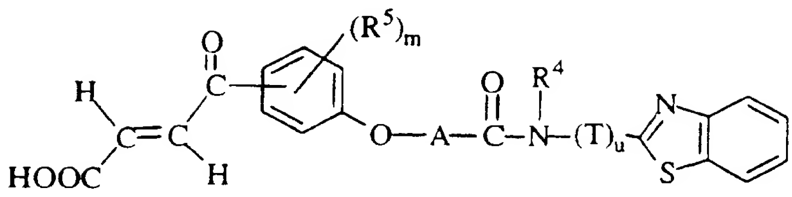
R^5: $-N(CH_3)_2$ (2-position)

A: $-CH_2-$ m: 1 R^4: H

Position of $-COCH=CHCOOH$: 4-position

NMR (48) Crystalline form: Pale yellow powder Form: Free

Table 159



Example 378

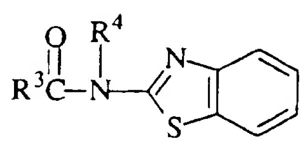
R^5: $-OCH_3$ (3-position)

A: $-CH_2-$ m: 1 R^4: H T: $-CH_2-$ u: 1

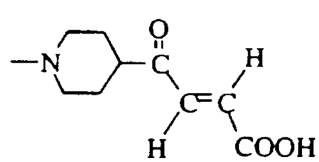
Position of –COCH=CHCOOH: 4-position

NMR (49) Crystalline form: Yellow powder Form: Free

Table 160



Example 379

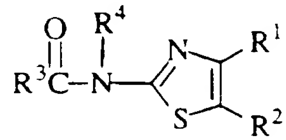
R^4: H R^3: 

M.p. 211.5-213°C Crystalline form: White powder Form: Free

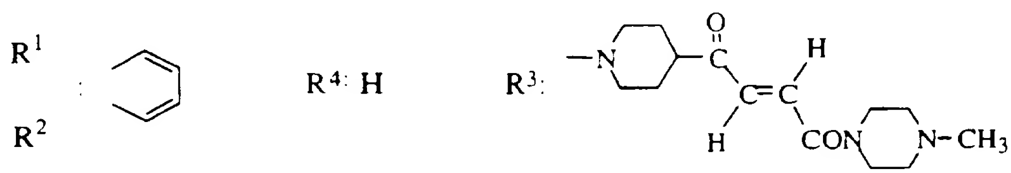
Solvent for recrystallization: Dimethylformamide-methanol

Using the suitable starting compounds, the compounds as listed in Tables 161-193 are obtained in the same manner as in Example 3 or 4.

Table 161



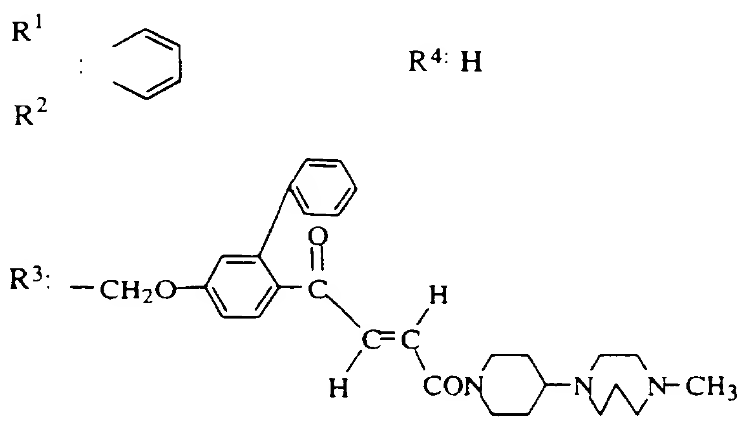
Example 380



M.p. 187.5-188.5°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-diethyl ether Form: Free

Example 381

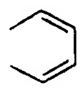


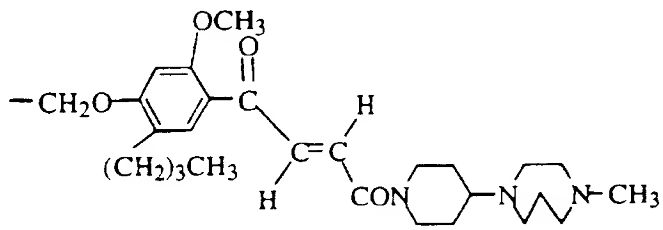
M.p. 164-166°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

Table 162

Example 382

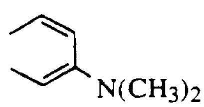
R^1 : 
R^2

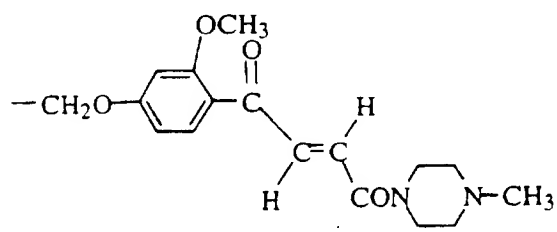
R^3: 

R^4: H M.p. 148.4-151.2°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

Example 383

R^1 : 
R^2

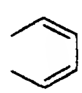
R^3: 

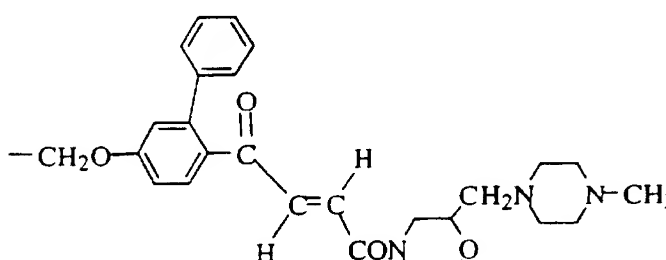
R^4: H M.p. 200-210°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl-H_2O

NMR (1)

Example 384

R^1 : 
R^2

R^3: 

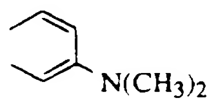
R^4: H M.p. 160.2-162.3°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

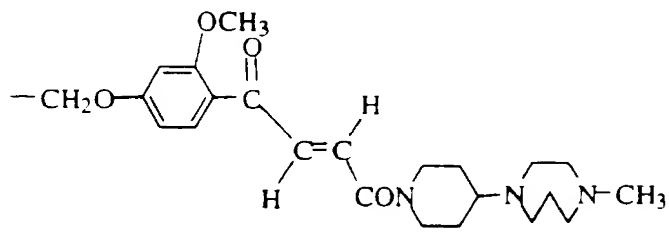
Table 163

Example 385

R^1 R^2 :



R^3:



R^4: H M.p. 156-166°C (decomp.) Crystalline form: Pale brown powder

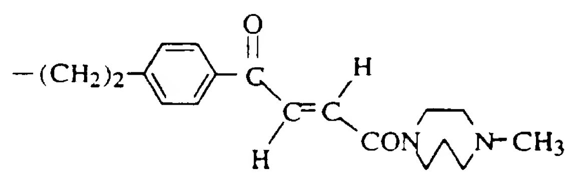
Solvent for recrystallization: Ethanol-water-diethyl ether Form: $3HCl \cdot 3H_2O$

NMR (2)

Example 386

R^1 R^2 :

R^3:

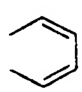


R^4: H M.p. 178-179°C Crystalline form: Pale yellow powder

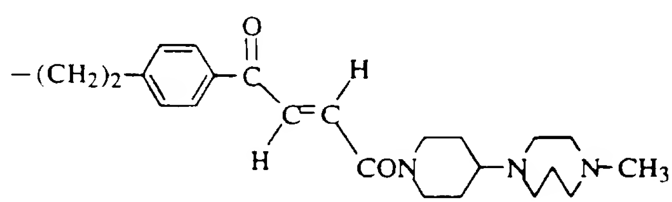
Solvent for recrystallization: Ethanol Form: Free

Example 387

R^1 R^2 :



R^3:

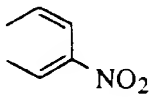


R^4: H M.p. 252-253.5°C Crystalline form: White powder

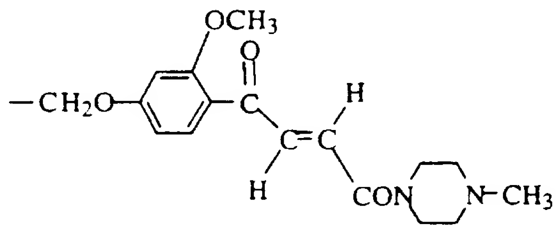
Solvent for recrystallization: Ethanol-water-diethyl ether Form: Free

Table 164

Example 388

R^1 : 

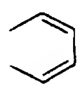
R^2

R^3: 

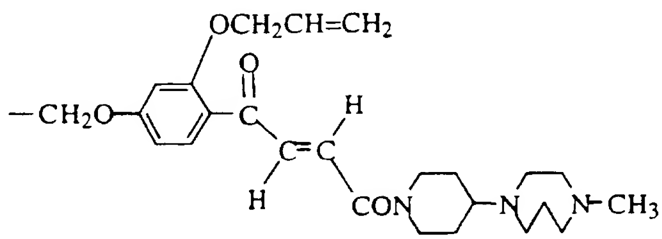
R^4: H M.p. 244-246°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Ethanol-chloroform Form: Free

Example 389

R^1 : 

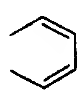
R^2

R^3: 

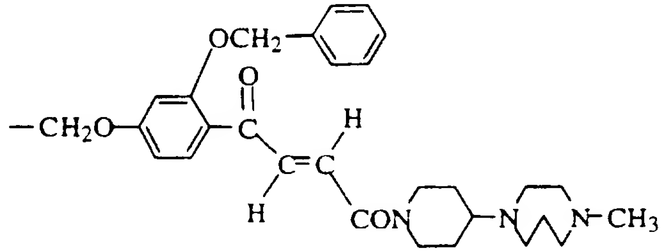
R^4: H M.p. 173-176°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Example 390

R^1 : 

R^2

R^3: 

R^4: H M.p. 161.2-163.0°C Crystalline form: Pale yellow powder

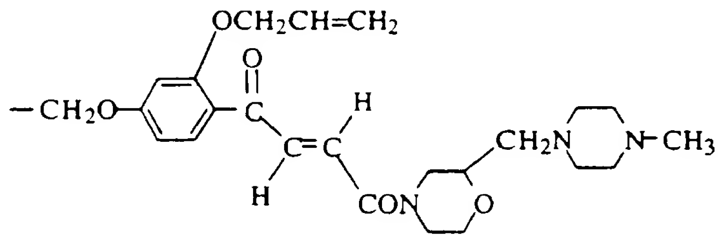
Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Table 165

Example 391

R^1 : 

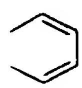
R^2

R^3: 

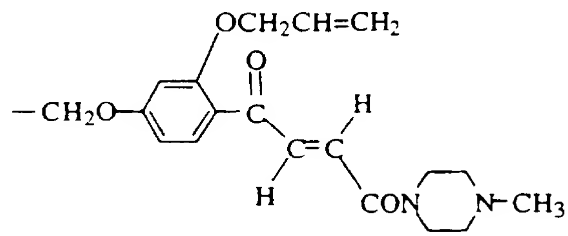
R^4: H M.p. 172-176°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: Free

Example 392

R^1 : 

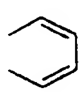
R^2

R^3: 

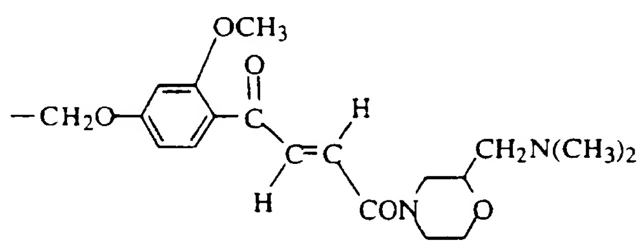
R^4: H M.p. 234.5-236.5°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

Example 393

R^1 : 

R^2

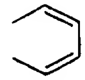
R^3: 

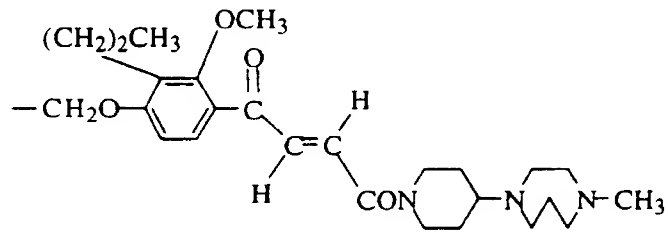
R^4: H M.p. 114-117°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: Methanesulfonate

Table 166

Example 394

R^1 R^2 : 

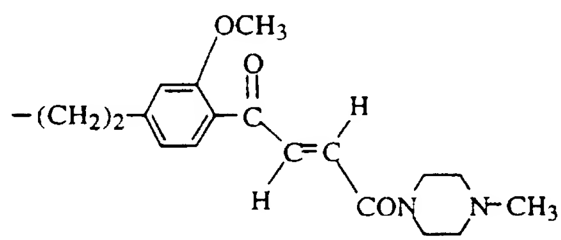
R^3: 

R^4: H M.p. 167.0-168.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 395

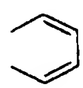
R^1 R^2 : 

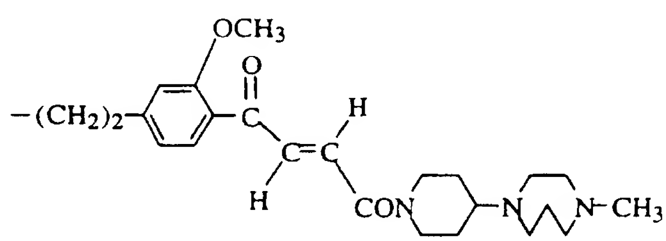
R^3: 

R^4: H M.p. 183-183.5°C Crystalline form: Pale brown powder

Solvent for recrystallization: Ethanol Form: Free

Example 396

R^1 R^2 : 

R^3: 

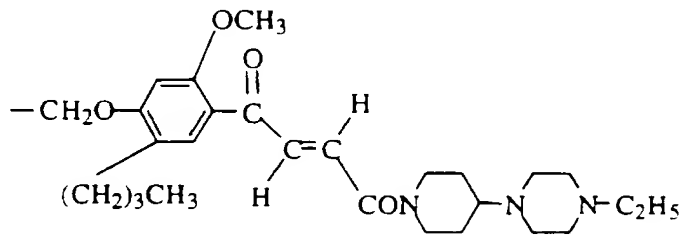
R^4: H M.p. 237.5-238.5°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 167

Example 397

R^1 R^2 : 

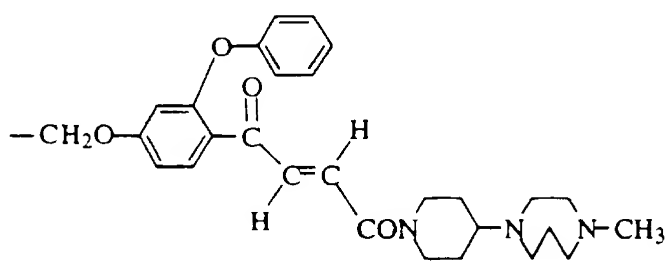
R^3: 

R^4: H M.p. 158.0-161.0°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 398

R^1 R^2 : 

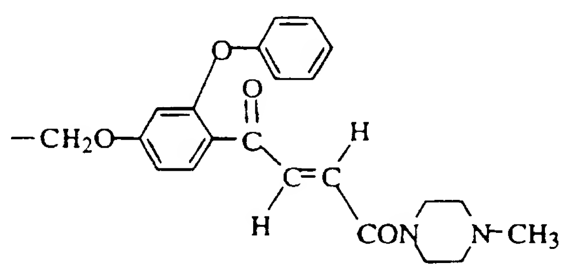
R^3: 

R^4: H M.p. 162.0-164.3°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 399

R^1 R^2 : 

R^3: 

R^4: H M.p. 133-136°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

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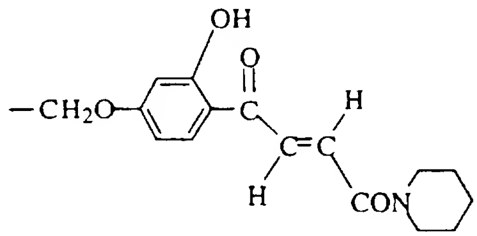
Table 168

Example 400

R^1 : 

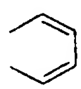
R^2

R^3: 

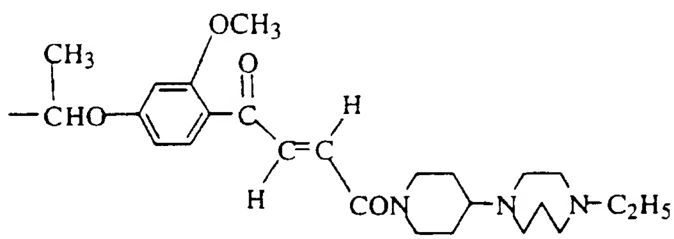
R^4: H M.p. 207.3-210.0°C Crystalline form: Yellow powder

Solvent for recrystallization: Dimethylformamide-ethanol Form: Free

Example 401

R^1 : 

R^2

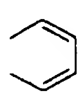
R^3: 

R^4: H M.p. 220-240°C (decomp.) Crystalline form: Pale yellow powder

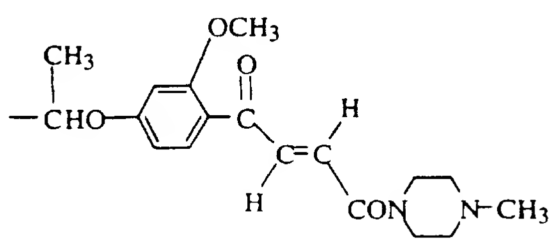
Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

NMR (3)

Example 402

R^1 : 

R^2

R^3: 

R^4: H M.p. 170-180°C (decomp.) Crystalline form: Pale yellow powder

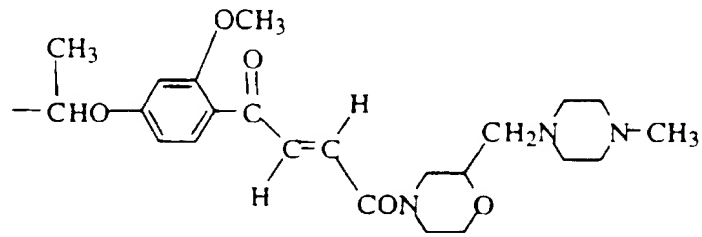
Solvent for recrystallization: Ethanol-diethyl ether Form: HCl

NMR (4)

Table 169

Example 403

R[1] :  R[2]

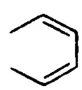
R[3]: 

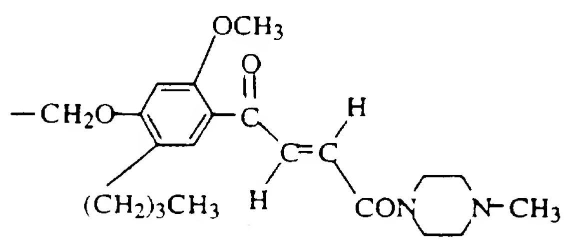
R[4]: H M.p. 190-220°C (decomp.) Crystalline form: Pale orange powder

Solvent for recrystallization: Ethanol-diethyl ether Form: 2HCl

NMR (5)

Example 404

R[1] :  R[2]

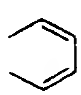
R[3]: 

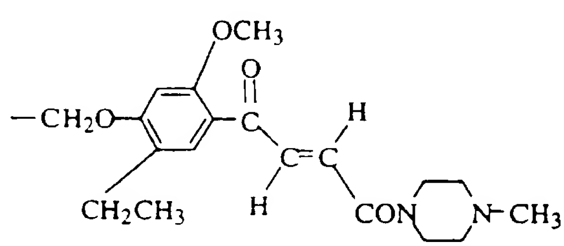
R[4]: H M.p. 138.5-140.3°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether

Form: Methanesulfonate

Example 405

R[1] :  R[2]

R[3]: 

R[4]: H M.p. 217.4-219.0°C Crystalline form: Yellow powder

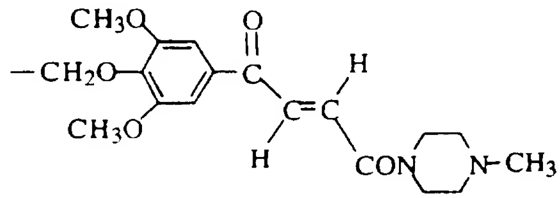
Solvent for recrystallization: Ethanol-diethyl ether-dichloromethane

Form: Methanesulfonate

Table 170

Example 406

R[1] : 
R[2]

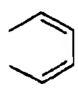
R[3]: 

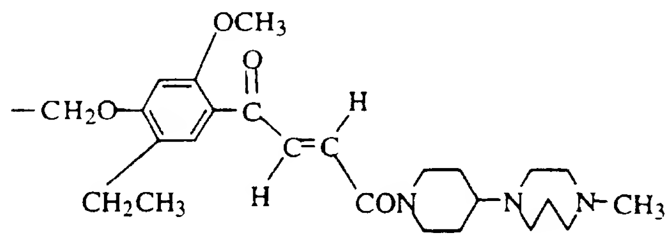
R[4]: H M.p. 138.2-139.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether

Form: Methanesulfonate

Example 407

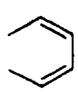
R[1] : 
R[2]

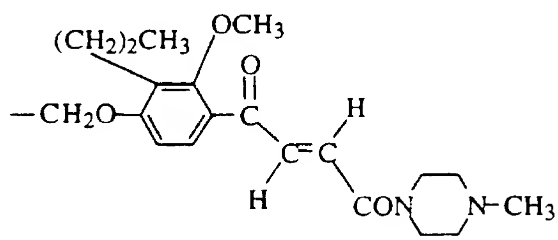
R[3]: 

R[4]: H M.p. 168.5-171.0°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Example 408

R[1] : 
R[2]

R[3]: 

R[4]: H M.p. 132-134°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-diethyl ether

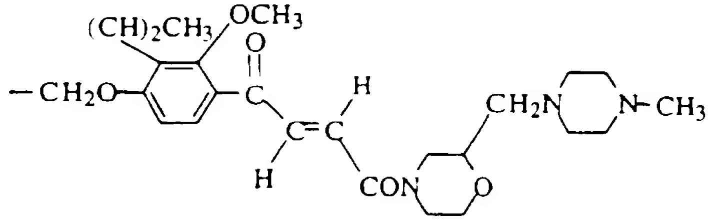
Form: Methanesulfonate

Table 171

Example 409

R^1 : 

R^2

R^3: 

R^4: H M.p. 190-193°C Crystalline form: Yellow powder

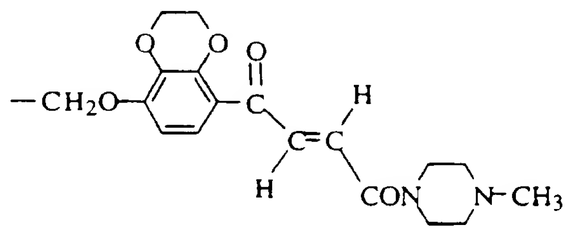
Solvent for recrystallization: Ethanol-acetone-diethyl ether

Form: 2HCl

Example 410

R^1 : 

R^2

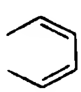
R^3: 

R^4: H M.p. 110-150°C (decomp.) Crystalline form: Pale yellow powder

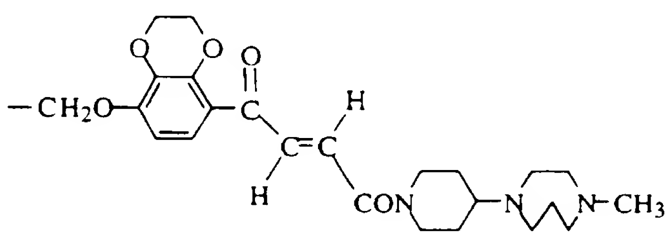
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

Form: Dimethanesulfonate NMR (6)

Example 411

R^1 : 

R^2

R^3: 

R^4: H M.p. 190-240°C (decomp.) Crystalline form: Pale yellow powder

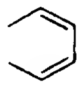
Solvent for recrystallization: Ethanol-diethyl ether

Form: 2HCl NMR (7)

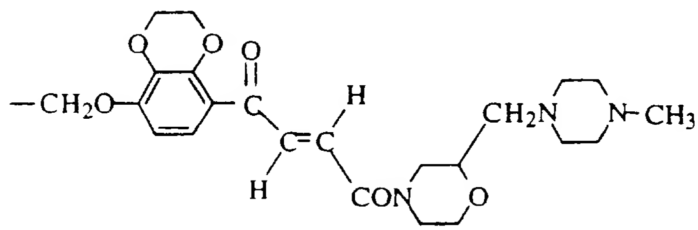
Table 172

Example 412

R^1

: 

R^2

R^3: 

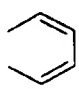
R^4: H M.p. 190-210°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether

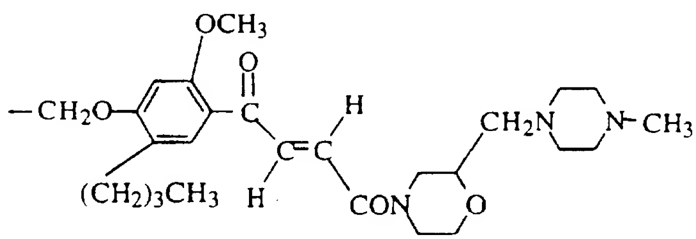
Form: 2HCl NMR (8)

Example 413

R^1

: 

R^2

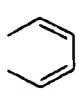
R^3: 

R^4: H M.p. 167.0-169.0°C Crystalline form: Yellow powder

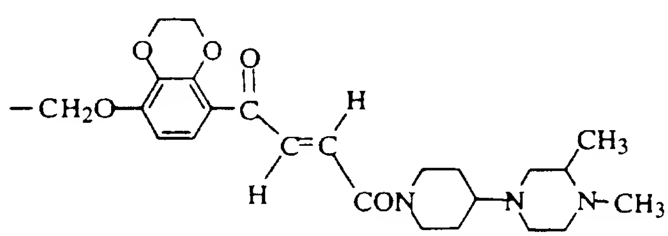
Solvent for recrystallization: Ethanol Form: 2HCl

Example 414

R^1

: 

R^2

R^3: 

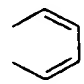
R^4: H M.p. 200-220°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether

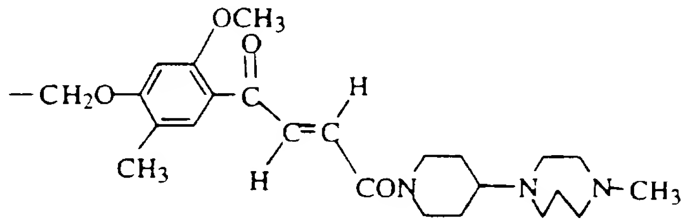
Form: 2HCl NMR (9)

Table 173

Example 415

R^1 : 

R^2

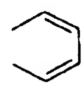
R^3: 

R^4: H M.p. 177-180°C Crystalline form: Yellow powder

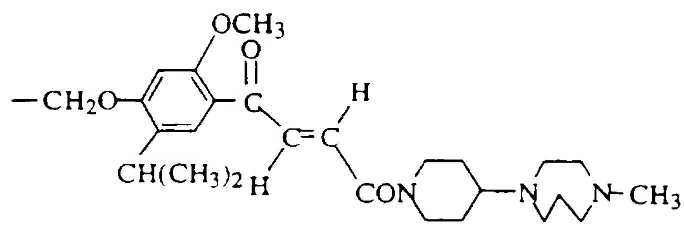
Solvent for recrystallization: Dichloromethane-diisopropyl ether

Form: 2HCl

Example 416

R^1 : 

R^2

R^3: 

R^4: H M.p. 179-182°C Crystalline form: Yellow powder

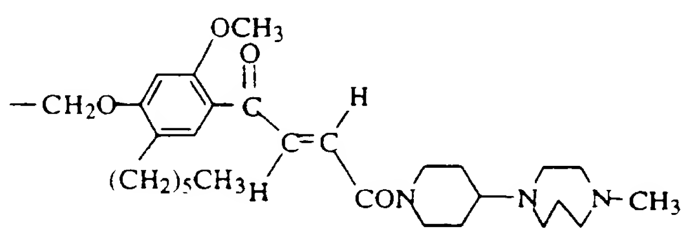
Solvent for recrystallization: Dichloromethane-diisopropyl ether

Form: 2HCl

Example 417

R^1 : 

R^2

R^3: 

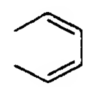
R^4: H M.p. 158-159°C Crystalline form: Yellow powder

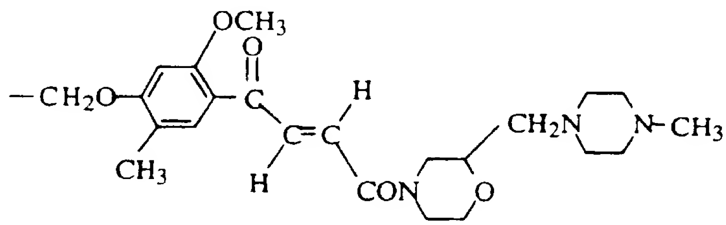
Solvent for recrystallization: Dichloromethane-diisopropyl ether

Form: 2HCl

Table 174

Example 418

R^1 :  R^2

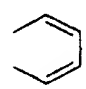
R^3: 

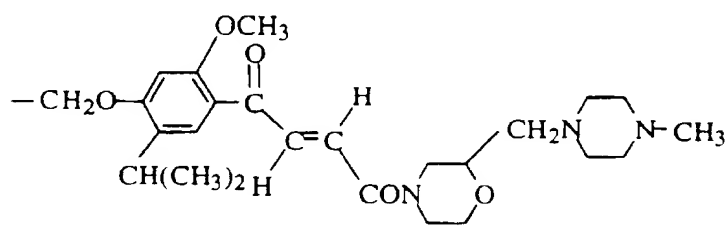
R^4: H M.p. 230-232°C Crystalline form: Yellow powder

Solvent for recrystallization: Methanol-diethyl ether

Form: 2HCl

Example 419

R^1 :  R^2

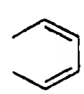
R^3: 

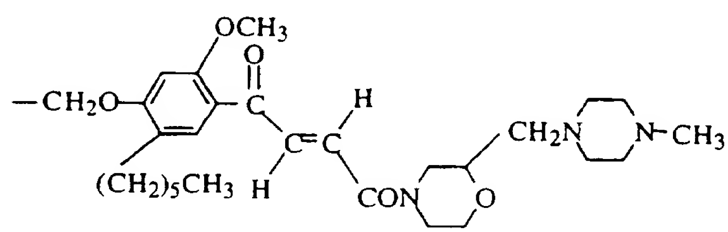
R^4: H M.p. 221-224°C Crystalline form: Yellow powder

Solvent for recrystallization: Methanol-diethyl ether

Form: 2HCl

Example 420

R^1 :  R^2

R^3: 

R^4: H M.p. 179-182°C Crystalline form: Yellow powder

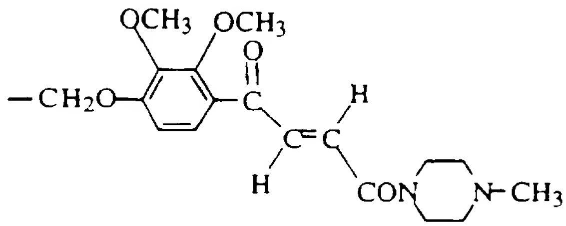
Solvent for recrystallization: Methanol-diethyl ether

Form: 2HCl

Table 175

Example 421

R^1 / R^2 : 

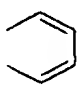
R^3: 

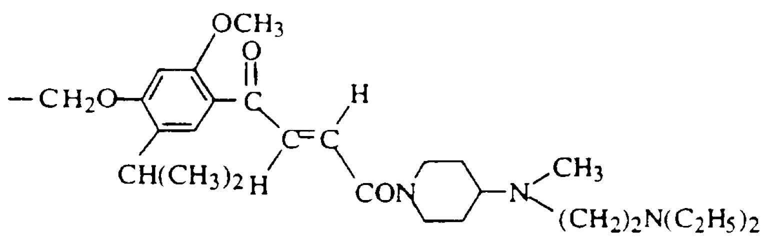
R^4: H M.p. 146.2-148.5°C Crystalline form:Gray powder

Solvent for recrystallization: Ethanol

Form: HCl

Example 422

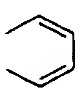
R^1 / R^2 : 

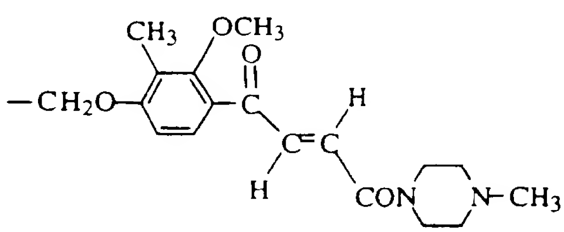
R^3: 

R^4: H M.p. 153-155°C Crystalline form: Yellow powder

Solvent for recrystallization: Dichloromethane Form: 2HCl

Example 423

R^1 / R^2 : 

R^3: 

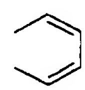
R^4: H M.p. 225-228°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol Form: Methanesulfonate

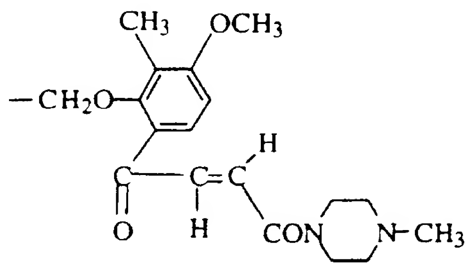
Table 176

Example 424

R^1

: 

R^2

R^3: 

R^4: H NMR (10) Crystalline form: Pale yellow amorphous

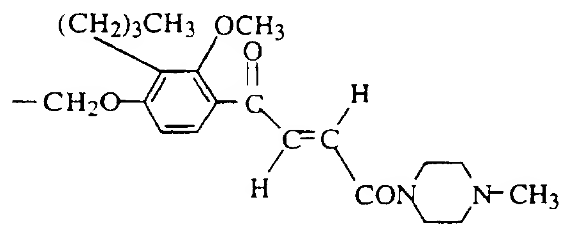
Form: Methanesulfonate

Example 425

R^1

: 

R^2

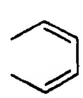
R^3: 

R^4: H M.p. 140-143°C Crystalline form: Pale yellow powder

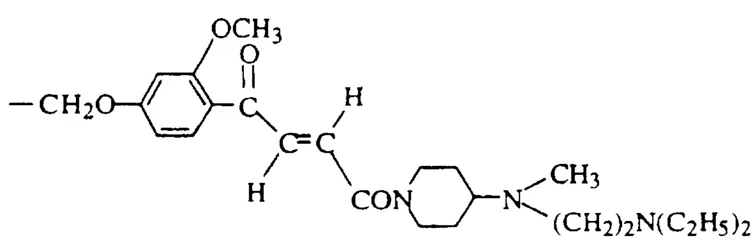
Solvent for recrystallization: Ethanol Form: Methanesulfonate

Example 426

R^1

: 

R^2

R^3: 

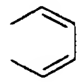
R^4: H M.p. 152.4-154.8°C Crystalline form: Pale yellow powder

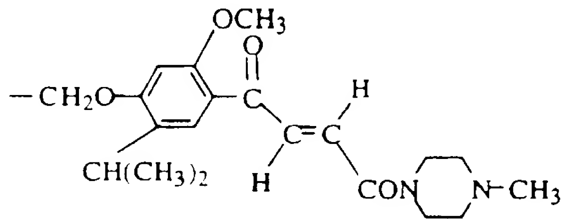
Solvent for recrystallization: Acetone-dichloromethane-water

Form: 2HCl

Table 177

Example 427

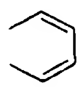
R^1 : 
R^2

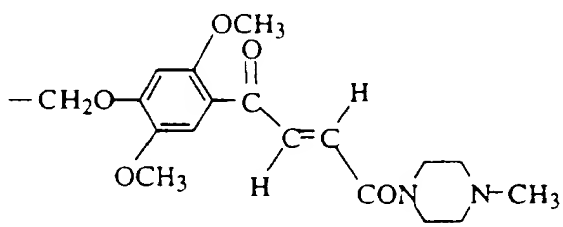
R^3: 

R^4: H M.p. 154-155°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: Methanesulfonate

Example 428

R^1 : 
R^2

R^3: 

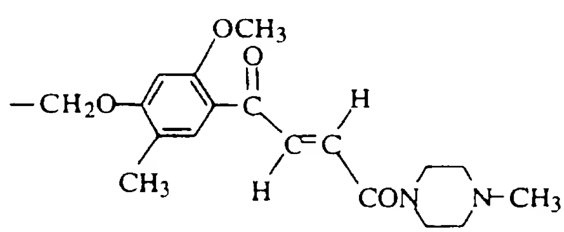
R^4: H M.p. 165-168°C Crystalline form: Yellow powder

Solvent for recrystallization: Dichloromethane-diethyl ether

Form: Methanesulfonate

Example 429

R^1 : 
R^2

R^3: 

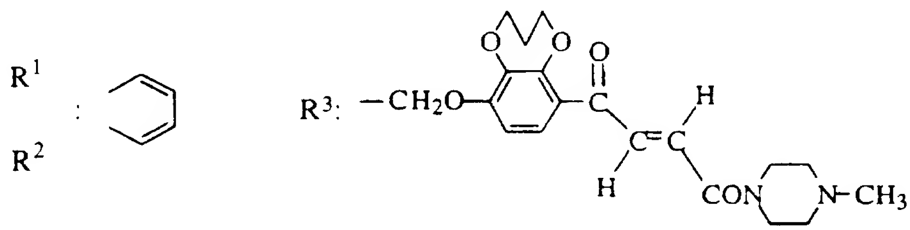
R^4: H M.p. 234-235°C Crystalline form: Yellow powder

Solvent for recrystallization: Dichloromethane-diethyl ether

Form: Methanesulfonate

Table 178

Example 430

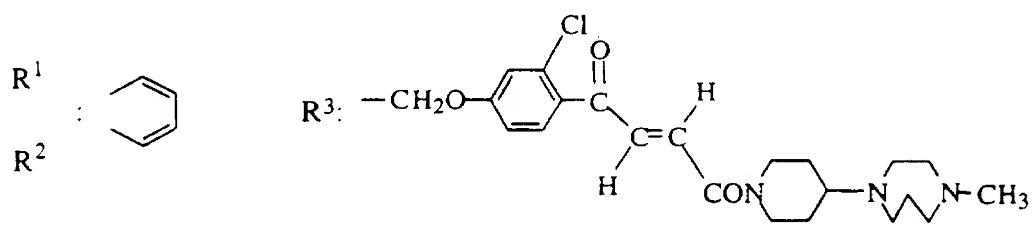


R⁴: H M.p. 195-200°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Acetone-water-diethyl ether

NMR (11) Form: Methanesulfonate

Example 431

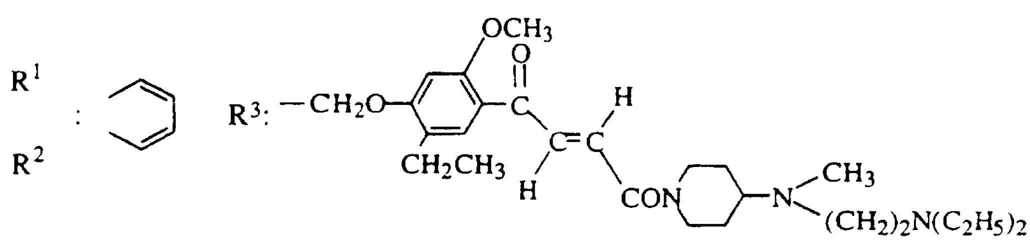


R⁴: H M.p. 183-220°C (decomp.) Crystalline form: White powder

Solvent for recrystallization: Acetone-ethanol-diethyl ether

NMR (12) Form: 2HCl

Example 432



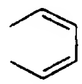
R⁴: H M.p. 159-161°C Crystalline form: Yellow powder

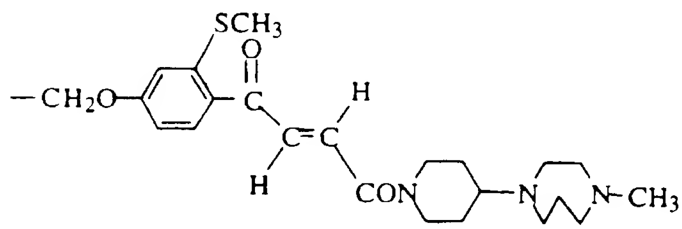
Solvent for recrystallization: Ethanol-acetone-diethyl ether

Form: 2HCl

Table 179

Example 433

R^1 :  R^2

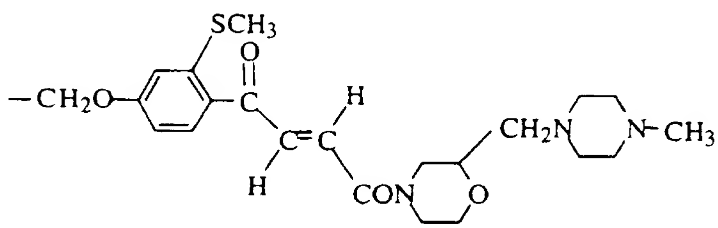
R^3: 

R^4: H M.p. 177-180°C Crystalline form: Yellow amorphous

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Example 434

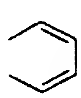
R^1 :  R^2

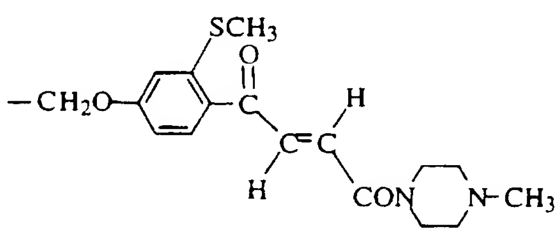
R^3: 

R^4: H M.p. 178-181°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 435

R^1 :  R^2

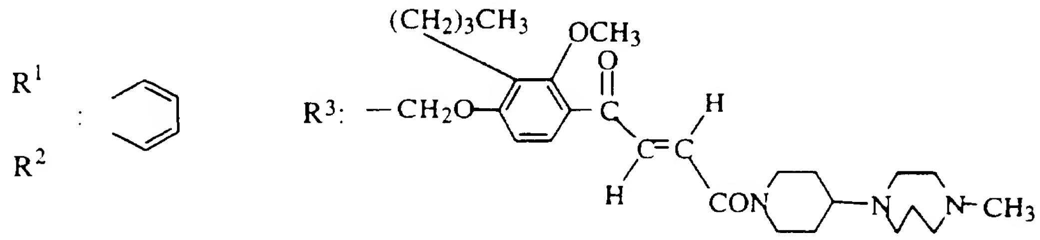
R^3: 

R^4: H M.p. 199-202°C Crystalline form: Pale orange powder

Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

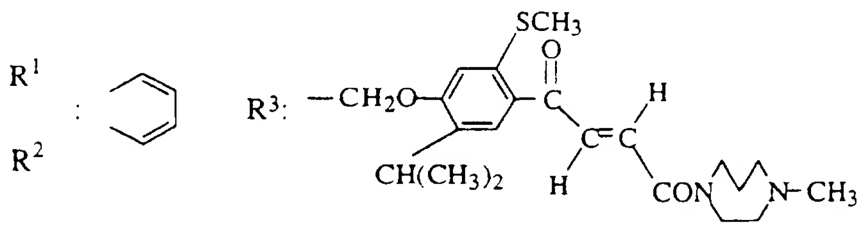
Table 180

Example 436



R^4: H NMR (13) Crystalline form: Yellow amorphous Form: 2HCl

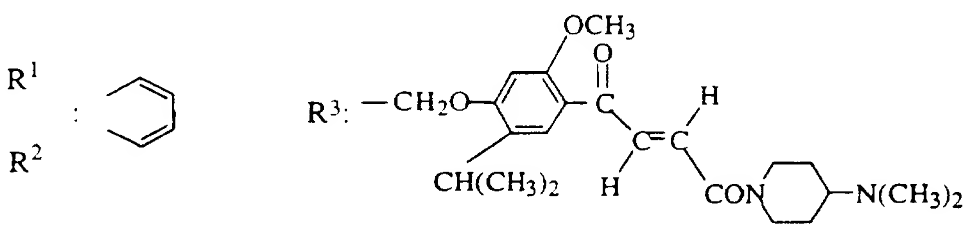
Example 437



R^4: H M.p. 151-154°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-diethyl ether Form: Methanesulfonate

Example 438

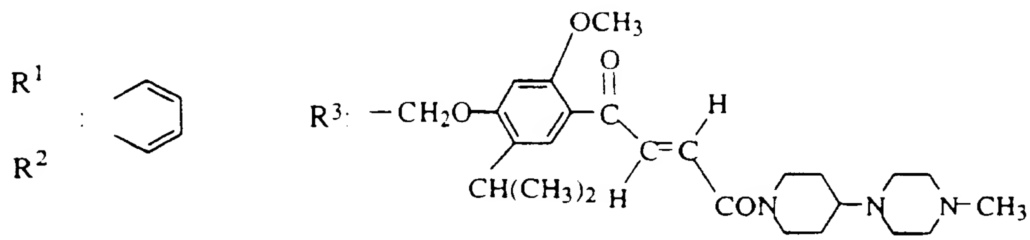


R^4: H M.p. 114-116°C Crystalline form: Yellow powder

Solvent for recrystallization: Acetone-water Form: Methanesulfonate

Table 181

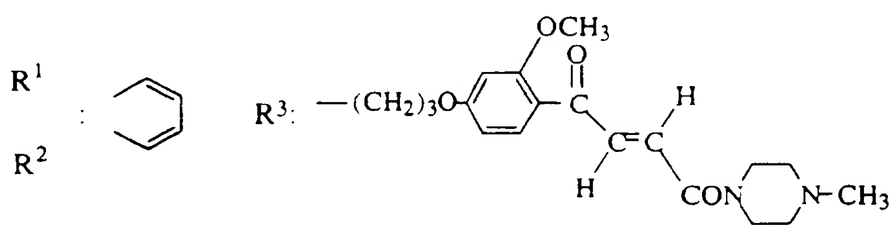
Example 439



R4: H M.p. 205-208°C Crystalline form: Yellow powder

Solvent for recrystallization: Acetone-water Form: 2HCl

Example 440

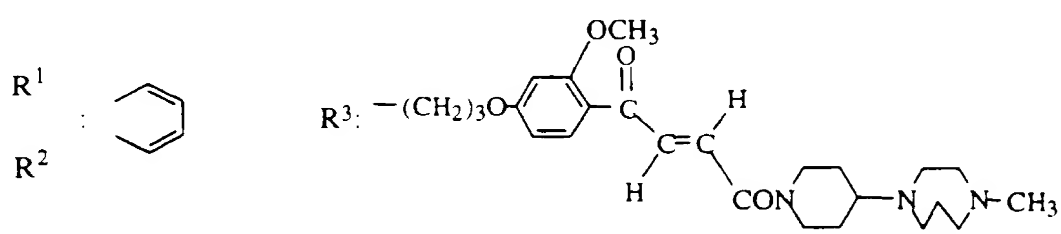


R4: H M.p. 185-190°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (14) Form: Methanesulfonate

Example 441



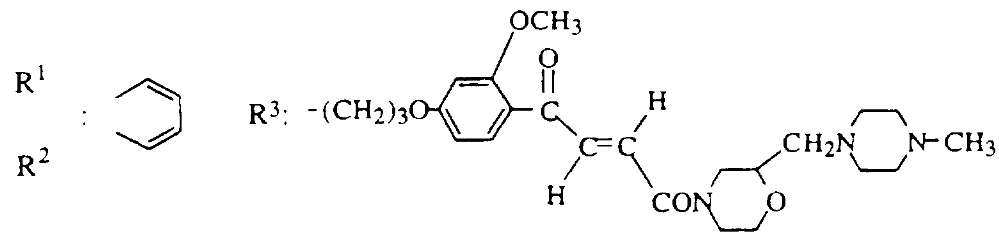
R4: H M.p. 160-180°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (15) Form: 2HCl

Table 182

Example 442

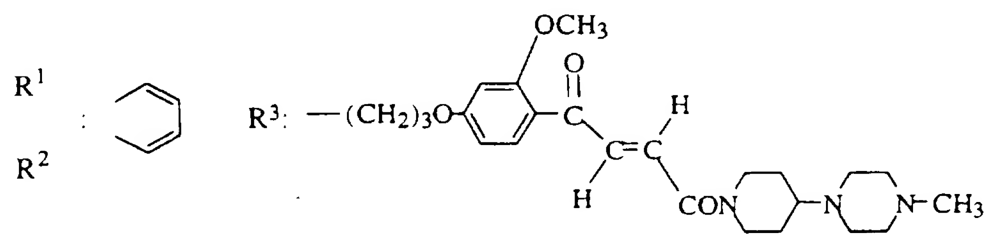


R^4: H M.p. 170-190°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (16) Form: 2HCl

Example 443

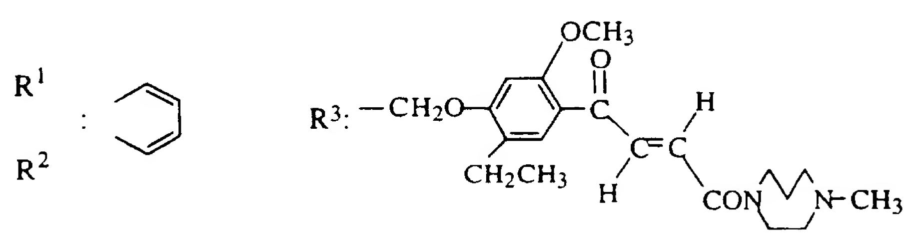


R^4: H M.p. 178-183°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (17) Form: 2HCl

Example 445



R^4: H M.p. 138-150°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

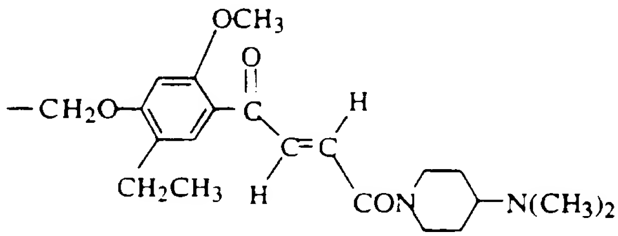
NMR (18) Form: Methanesulfonate

Table 183

Example 446

R^1 : 

R^2

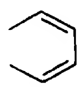
R^3: 

R^4: H M.p. 120-160°C (decomp.) Crystalline form: Pale brown powder

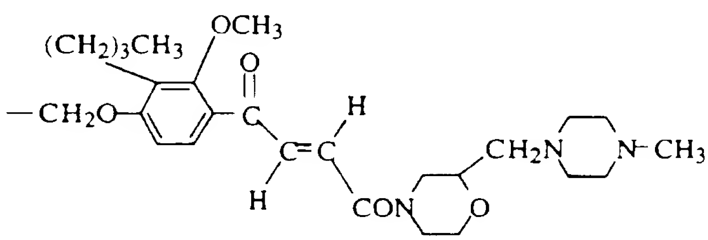
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether-acetone

NMR (19) Form: Methanesulfonate

Example 447

R^1 : 

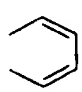
R^2

R^3: 

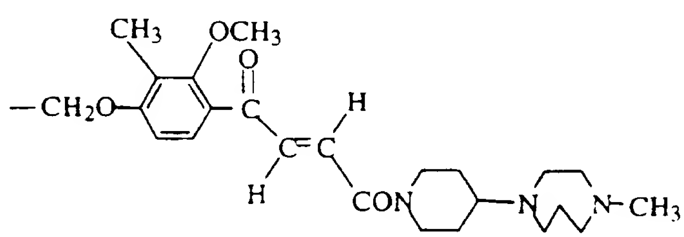
R^4: H M.p. 169-171°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 448

R^1 : 

R^2

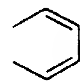
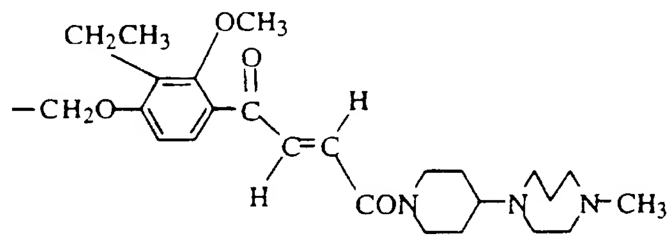
R^3: 

R^4: H M.p. 178-180°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether Form: 2HCl

Table 184

Example 449

R^1 :  R^3: 

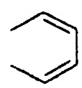
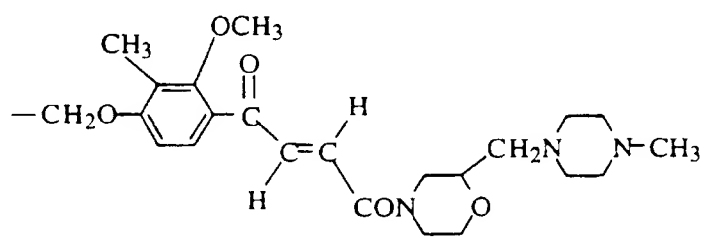
R^2

R^4: H M.p. 162-164°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether

Form: 2HCl

Example 450

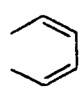
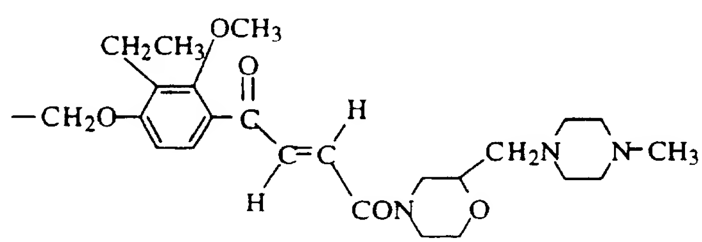
R^1 :  R^3: 

R^2

R^4: H M.p. 172-175°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 451

R^1 :  R^3: 

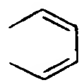
R^2

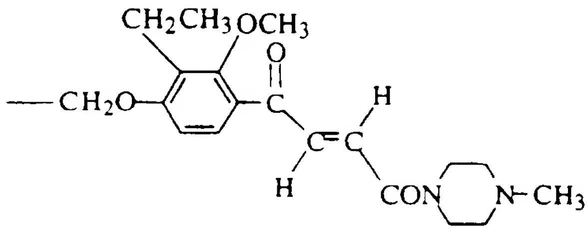
R^4: H M.p. 167-170°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 185

Example 452

R^1 R^2 : 

R^3: 

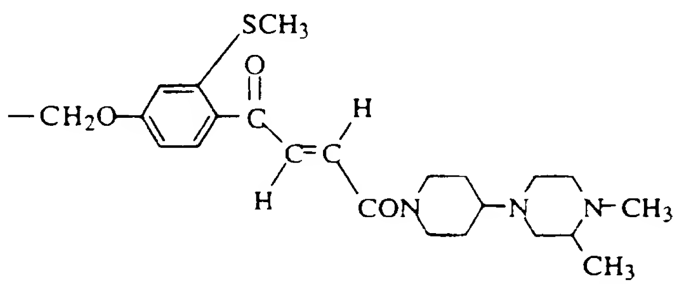
R^4: H M.p. 208-209°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water

Form: Methanesulfonate

Example 453

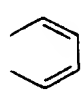
R^1 R^2 : 

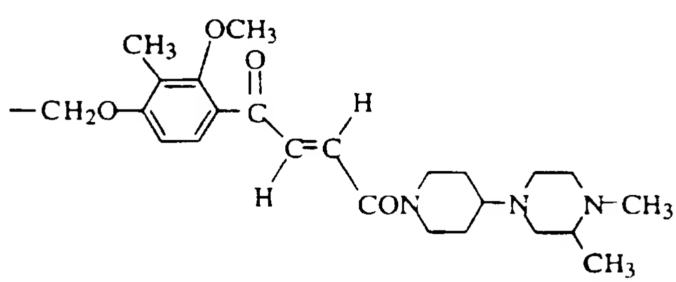
R^3: 

R^4: H M.p. 246-249°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 454

R^1 R^2 : 

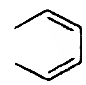
R^3: 

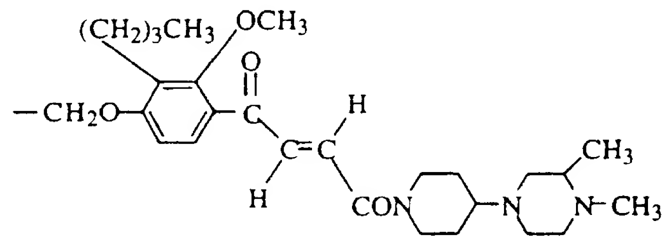
R^4: H M.p. 188-190°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Table 186

Example 455

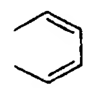
R^1 :  R^2

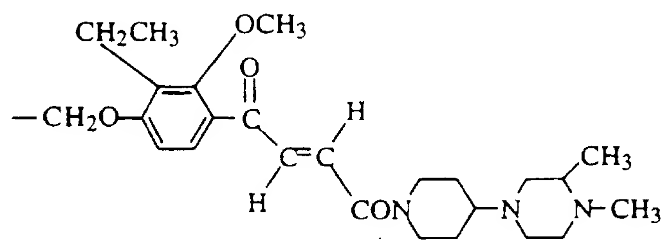
R^3: 

R^4: H M.p. 167-169°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 456

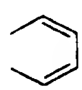
R^1 :  R^2

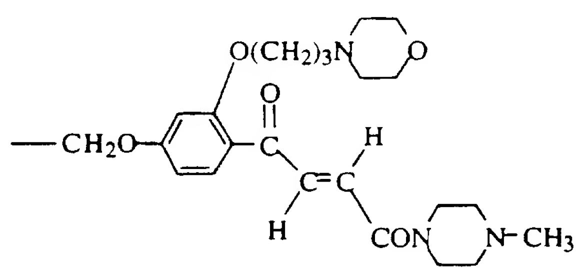
R^3: 

R^4: H M.p. 170-173°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water Form: 2HCl

Example 457

R^1 :  R^2

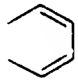
R^3: 

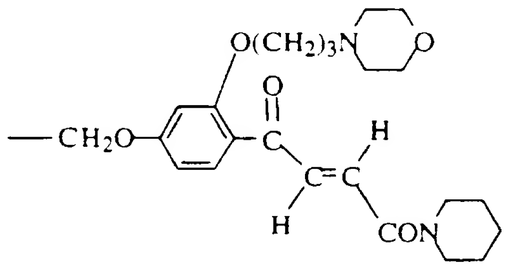
R^4: H M.p. 225-228°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane Form: 2HCl

Table 187

Example 458

R^1
: 
R^2

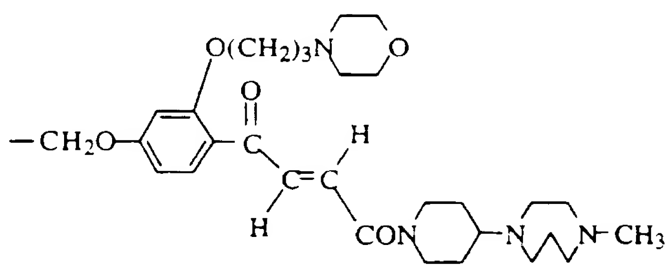
R^3: 

R^4: H M.p. 162.0-163.5°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water Form: Methanesulfonate

Example 459

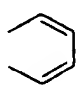
R^1
: 
R^2

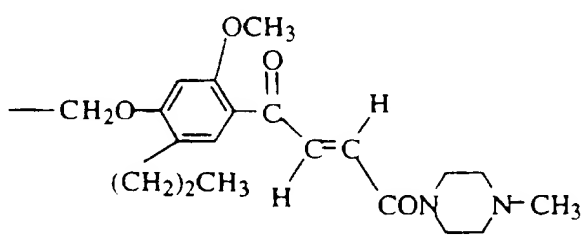
R^3: 

R^4: H M.p. 9.5-212.5°C Crystalline form: White powder

Solvent for recrystallization: Ethanol-water Form: 3HCl

Example 460

R^1
: 
R^2

R^3: 

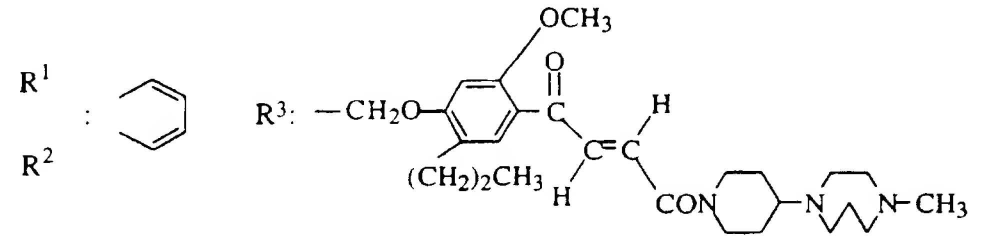
R^4: H M.p. 155-185°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (20) Form: Methanesulfonate

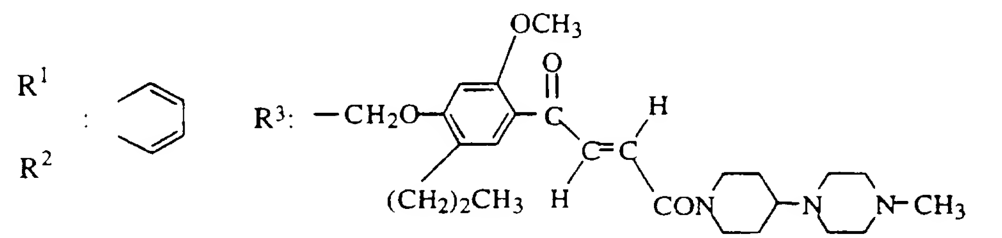
Table 188

Example 461



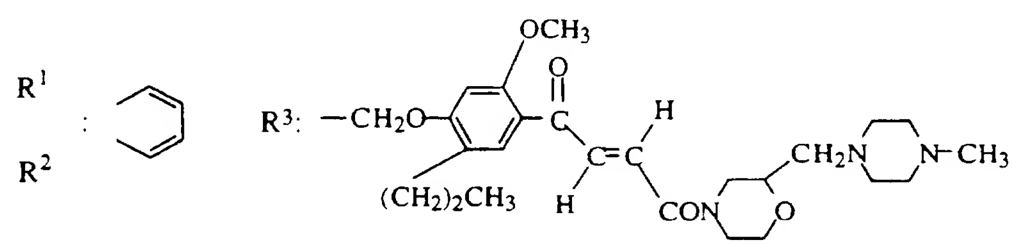
R4: H M.p. 180-215°C (decomp.) Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether
NMR (21) Form: 2HCl

Example 462



R4: H M.p. 220-225°C (decomp.) Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether
NMR (22) Form: 2HCl

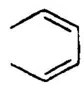
Example 463

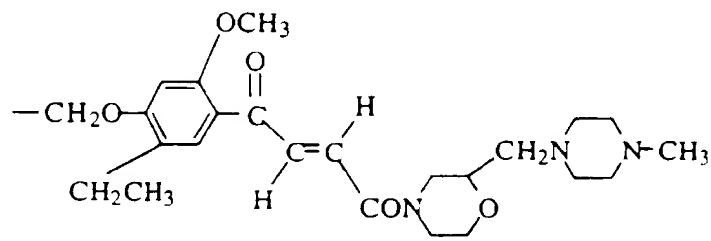


R4: H M.p. 180-215°C (decomp.) Crystalline form: Pale yellow powder
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether
NMR (23) Form: 2HCl

Table 189

Example 464

R^1 :  R^2

R^3: 

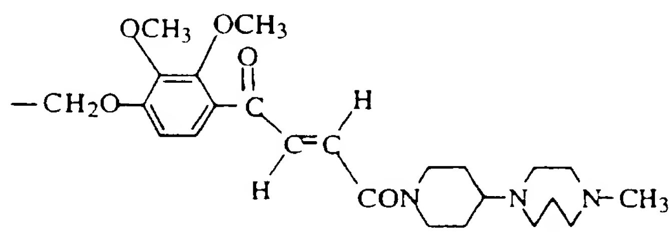
R^4: H M.p. 185.5-192°C Crystalline form: Yellow powder

Solvent for recrystallization: Ethanol-water

NMR (24) Form: 2HCl

Example 465

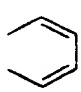
R^1 :  R^2

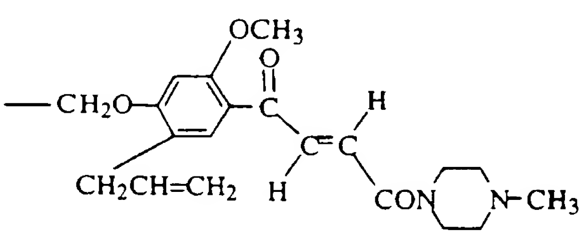
R^3: 

R^4: H M.p. 159.5-161.2°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether-water Form: 2HCl

Example 466

R^1 :  R^2

R^3: 

R^4: H M.p. 150-158°C (decomp.) Crystalline form: Pale yellow powder

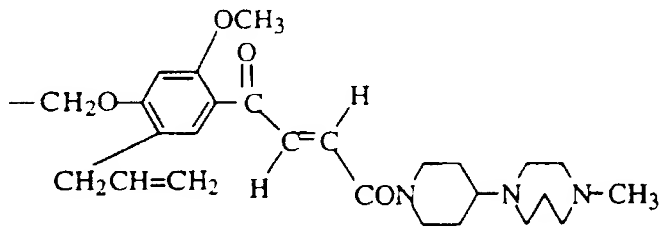
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (25) Form: Methanesulfonate

Table 190

Example 467

R1 R2 : 

R3: 

R4: H M.p. 193-204°C (decomp.)

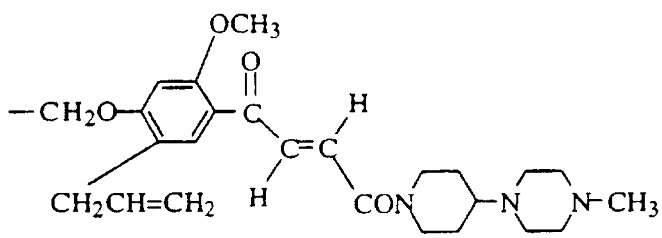
Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (26) Form: 2HCl

Example 468

R1 R2 : 

R3: 

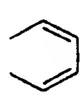
R4: H M.p. 205-213°C (decomp.)

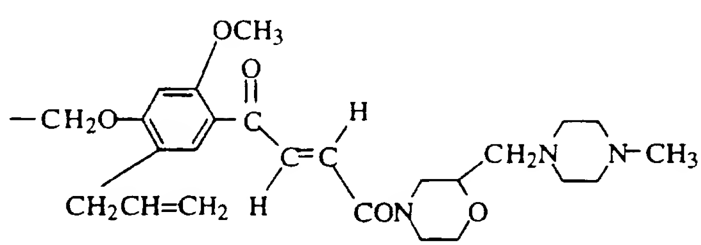
Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (27) Form: 2HCl

Example 469

R1 R2 : 

R3: 

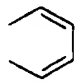
R4: H M.p. 205-213°C (decomp.) Crystalline form: Pale yellow powder

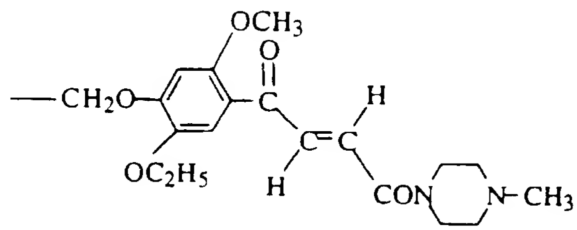
Solvent for recrystallization: Ethanol-dichloromethane-diethyl ether

NMR (28) Form: 2HCl

Table 191

Example 470

R^1 R^2 : 

R^3: 

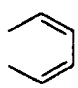
R^4: H M.p. 131-160°C (decomp.)

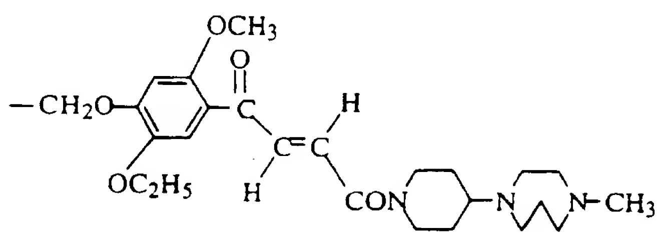
Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

NMR (29) Form: Methanesulfonate

Example 471

R^1 R^2 : 

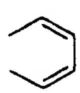
R^3: 

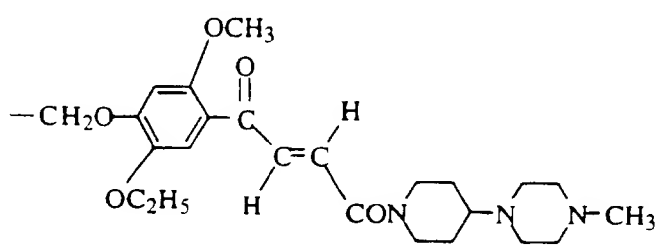
R^4: H M.p. 180-210°C (decomp.) Crystalline form: Pale brown powder

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

NMR (30) Form: 2HCl

Example 472

R^1 R^2 : 

R^3: 

R^4: H M.p. 231-235°C (decomp.) Crystalline form: Pale yellow powder

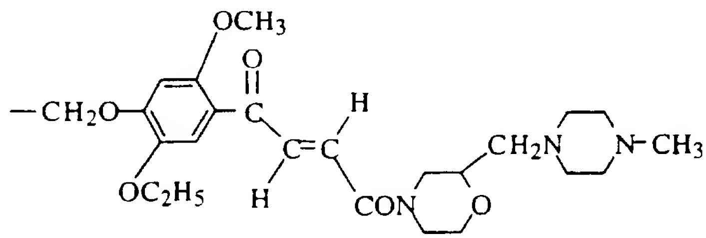
Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

Form: 2HCl

Table 192

Example 473

R^1 :  R^2

R^3: 

R^4: H M.p. 216-221°C (decomp.)

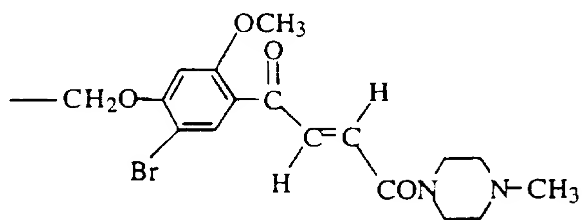
Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

NMR (31) Form: 2HCl

Example 474

R^1 :  R^2

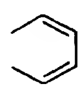
R^3: 

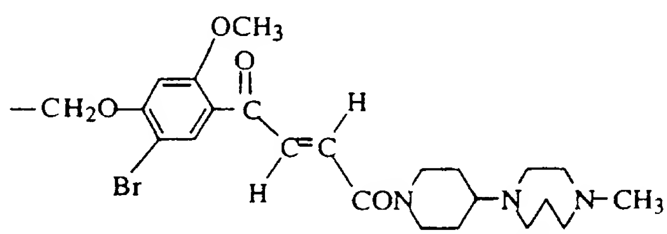
R^4: H M.p. 175-205°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

NMR (32) Form: Methanesulfonate

Example 475

R^1 :  R^2

R^3: 

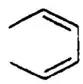
R^4: H M.p. 185-230°C (decomp.) Crystalline form: Pale yellow powder

Solvent for recrystallization: Dichloromethane-ethanol-diethyl ether

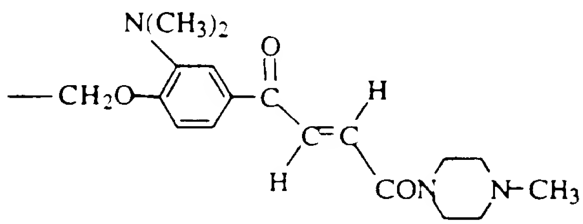
NMR (33) Form: 2HCl

Table 193

Example 476

R^1 : 

R^2

R^3: 

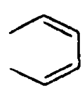
R^4: H M.p. 160-170°C

Crystalline form: Pale yellow powder

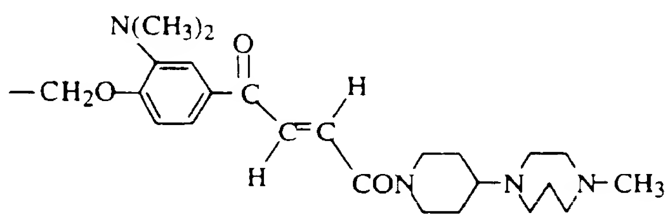
Solvent for recrystallization: Ethanol-water

NMR (34) Form: Dimethanesulfonate

Example 477

R^1 : 

R^2

R^3: 

R^4: H M.p. 172-178°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water NMR (35) Form: 3HCl

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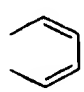
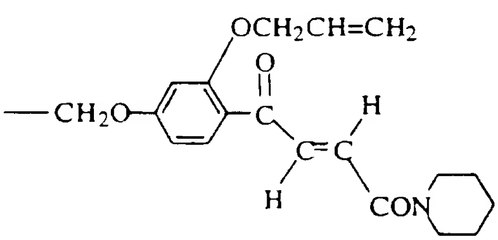
Example 478

R^1 : 

R^2

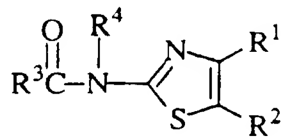
R^3: 

R^4: H M.p. 185.2-186.0°C Crystalline form: White powder

Solvent for recrystallization: Ethanol Form: Free

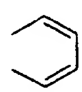
Using the suitable starting compounds, the compounds as listed in Table 194 are obtained in the same manner as in Example 8.

Table 194

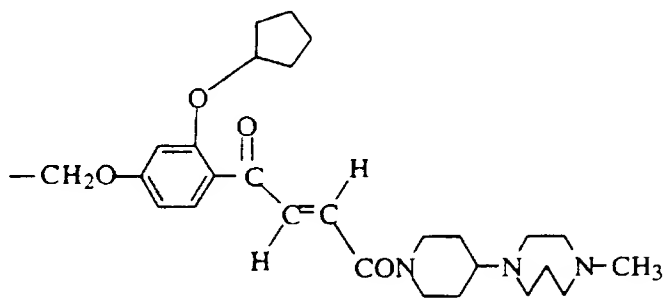


Example 479

R^1 : R^2



R^3:



R^4: H M.p. 171.5-173.0°C

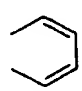
Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-diethyl ether-dichloromethane

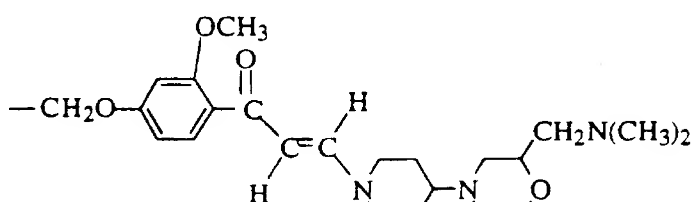
Form: 2HCl

Example 480

R^1 : R^2



R^3:

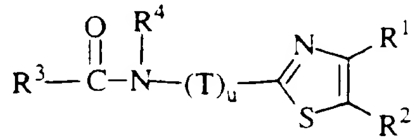


R^4: H M.p. 111.5-114.5°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-isopropyl alcohol Form: 2HCl

Using the suitable starting compounds, the compound as listed in Table 195 are obtained in the same manner as in Example 3 or 4.

Table 195



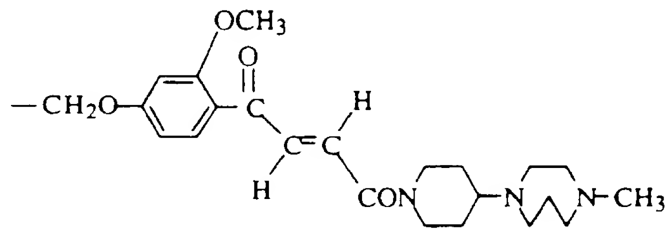
Example 481

R^1

:

R^2

R^3:



R^4: H T: $-CH_2-$ u: 1

M.p. 147-150°C Crystalline form: Pale yellow powder

Solvent for recrystallization: Ethanol-water-diethyl ether-isopropyl alcohol

Form: 2HCl

^{1}H-NMR spectrum (NMR (1) to NMR (49)) as described in Tables 150-195 are as follows:

NMR (1) (DMSO-d_6) δppm: 2.65-2.8 (4H, m), 3.06 (9H, s), 3.87 (3H, s), 4.15-4.65 (4H, m), 5.07 (2H, s), 6.70 (1H, dd, J=2Hz, J=8.5Hz), 6.81 (1H, d, J=2Hz), 7.29 (1H, d, J=15Hz), 7.48 (1H, br), 7.62 (1H, d, J=15Hz), 7.65 (1H, d, J=8.5Hz), 7.77 (1H, d, J=9Hz), 7.93 (1H, br), 11.0 (1H, br), 12.7 (1H,br)

NMR (2) (DMSO-d_6) δppm: 1.65 (2H, br), 2.05-2.40 (4H, m), 2.55-2.9 (4H, m), 3.13 (6H, s), 3.25-4.8 (15H, m), 5.10 (2H, s), 6.70 (1H, dd, J=2Hz, J=9Hz),

6.81 (1H, d, J=2Hz), 7.26 (1H, d, J=15Hz), 7.55 (1H, d, J=15Hz), 7.64 (1H, d, J=8.5Hz), 7.7-7.8 (1H, m), 7.88 (1H, d, J=9Hz), 8.31 (1H, br), 11.2-12.2 (2H, m)

NMR (3) (DMSO-d_6) δppm: 1.61 (3H, d, J=6.5Hz), 1.6 (2H, br), 2.12 (4H, br), 2.5-2.85 (4H, m), 2.95-4.05 (13H, m), 4.1-4.3 (1H, m), 4.4-4.7 (1H, m), 5.35 (1H, q, J=6.5Hz), 6.63 (1H, dd, J=2Hz, 9Hz), 6.77 (1H, d, J=2Hz), 7.15-7.7 (4H, m), 7.69 (1H, d, J=9Hz), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7.5Hz), 11.1-13.1 (3H, m)

NMR (4) (DMSO-d_6) δppm: 1.61 (3H, d, J=6.5Hz), 2.73 (3H, d, J=4Hz), 2.8-4.1 (6H, m), 3.85 (3H, s), 4.1-4.35 (1H, m), 4.35-4.6 (1H, m), 5.38 (1H, q, J=6.5Hz), 6.63 (1H, dd, J=2Hz, 9Hz), 6.78 (1H, d, J=2Hz), 7.26 (1H, d, J=15Hz), 7.25-7.5 (2H, m), 7.59 (1H, d, J=15Hz), 7.63(1H, d, J=9Hz), 7.76 (1H, d, J=7.5Hz), 7.97 (1H, d, J=7Hz), 11.40 (1H, br), 12.9 (1H, br)

NMR (5) (DMSO-d_6) δppm: 1.61 (3H, d, J=6.5Hz), 2.35-4.4 (23H, m), 5.37 (1H, q, J=6.5Hz), 6.63 (1H, dd, J=2Hz, J=8.5Hz), 6.78 (1H, d, J=2Hz), 7.1-7.7 (5H, m), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.85 (2H, br) 12.90 (1H, br)

NMR (6) (DMSO-d_6) δppm: 2.42 (6H, s), 2.82 (3H, d, J=4Hz), 2.9-3.25 (3H, m), 3.3-3.6 (3H, m), 4.15-4.6 (6H, m), 5.03 (2H, s), 6.68 (1H, d, J=9Hz), 7.23 (1H, d, J=9Hz), 7.31 (1H, d, J=15Hz), 7.15-7.5 (2H, m), 7.61 (1H, d, J=15Hz), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 9.85 (1H, br)

NMR (7) (DMSO-d_6) δppm: 1.64 (2H, br), 2.17 (4H, br), 2.55-2.7 (4H, m), 2.95-4.0 (10H, m), 4.05-4.7 (6H, m), 5.03 (2H, s), 6.68 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.25-7.6 (4H, m), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7.5Hz), 11.1-12.2 (2H, m), 12.65 (1H, br)

NMR (8) (DMSO-d_6) δppm: 2.55-2.7 (1H, m), 2.79 (3H, s), 2.85-4.5 (20H,

m), 5.04 (2H, s), 6.68 (1H, d, J=8.5Hz), 7.15-7.7 (5H, m), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.4 -13.1 (2H, m)

NMR (9) (DMSO-d_6) δppm: 1.35 (3H, d, J=5.5Hz), 1.64 (2H, br), 2.14 (2H, br), 2.55-2.95 (4H, m), 2.95-4.0 (9H, m), 6.0 (1H, d, J=9Hz), 7.22 (1H, d, J=9Hz), 7.29 (1H, d, J=15.5Hz), 4.05-4.7 (6H, m), 5.03 (2H, s), 7.4-7.5 (1H, m), 7.53 (1H, d, J=15.5Hz), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.5-13.0 (2H, m)

NMR (10) (DMSO-d_6) δppm; 2.16 (3H, s), 2.37 (3H, s), 2.77 (3H, d, J=4.2Hz), 2.83-3.19 (3H, m), 3.29-3.58 (3H, m), 3.88 (3H, s), 4.12-4.57 (2H, m), 4.65 (2H,s), 6.95 (1H, d, J=8.8Hz), 7.19-7.37 (2H, m), 7.37-7.50 (1H, m), 7.50-7.66 (2H, m), 7.75 (1H, d, J=7.9Hz), 7.99 (1H, d, J=7.9Hz), 9.82 (1H, brs), 11.95-12.71 (1H, m)

NMR (11) (DMSO-d_6) δppm; 2.17 (2H, br), 2.34 (3H, s), 2.82 (3H, s), 3.05 (4H, br), 3.4 (2H, br), 4.05-4.4 (5H, m), 4.49 (1H, br), 5.05 (2H, s), 6.83 (1H, d, J=9Hz), 7.28 (1H, d, J=15Hz), 7.29 (1H, d, J=9Hz), 7.25-7.35 (1H, m), 7.35-7.5 (1H, m), 7.52 (1H, d, J=15Hz), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 9.81 (1H, br), 12.6 (1H, br)

NMR (12) (DMSO-d_6) δppm; 1.61 (2H, br), 2.15 (4H, br), 2.55-2.9 (4H, m), 3.0-4.3 (11H, m), 4.4-4.7 (1H, m), 5.09 (2H, s), 7.12 (1H, dd, J=2.5Hz, J=8.5Hz), 7.25-7.41 (4H, m), 7.4-7.5 (1H, m), 7.69 (1H, d, J=8.5Hz), 7.77 (1H, d, J=7.5Hz), 7.99 (1H, d, J=7Hz), 11.0-12.2 (2H, m)

NMR (13) (DMSO-d_6) δppm; 0.91 (3H, t, J=7.2Hz), 1.2 1.86 (6H, m), 1.93-2.39 (4H, m), 2.58-2.89 (4H, m), 2.76 (3H, s), 2.95-3.98 (9H, m), 3.64 (3H, s), 4.07-4.31 (1H, m), 4.41-4.69 (1H, m), 5.09 (2H, s), 6.83 (1H, d, J=8.9Hz), 7.20-7.64 (5H, m), 7.76 (1H, d, J=7.9Hz), 7.97 (1H, d, J=7.9Hz), 11.11-12.29 (2H, m),

12.72 (1H, brs)

NMR (14) (DMSO-d_6) δppm; 2.0-2.2 (2H, m), 2.34 (3H,s), 2.68 (2H, t, J=7Hz), 2.81 (3H, d, J=3Hz), 2.9-3.2 (2H, m), 3.3-3.65 (4H, m), 3.79 (3H, s), 4.15 (2H, t, J=6Hz), 4.2-4.4 (1H, m), 4.4-4.6 (1H, m), 6.55-6.7 (2H, m), 7.2-7.35 (1H, m), 7.27 (1H, d, J=15Hz), 7.35-7.5 (1H, m), 7.63 (1H, d, J=9.5Hz), 7.63 (1H, d, J=15Hz), 7.72 (1H, d, J=7.5Hz), 7.9-8.0 (1H, m), 9.79 (1H, br), 12.38 (1H, br)

NMR (15) (DMSO-d_6) δppm; 1.64 (2H, br), 2.0-2.4 (6H, m), 2.55-2.9 (6H,m), 2.95-4.0 (3H, m), 4.0-4.35 (3H, m), 4.4-4.7 (1H, m), 6.55-6.75 (2H, m), 7.0 (1H, br), 7.2-7.35 (2H, m), 7.35-7.45 (1H, m), 7.5-7.65 (2H, m), 7.65-7.75 (1H, m), 7.9-8.0 (1H, m), 11.2-12.6 (2H, m)

NMR (16) (DMSO-d_6) δppm; 2.0-2.2 (2H, m), 2.69 (2H, t, J=7Hz), 2.80 (3H, s), 2.9-4.4 (22H, m), 6.4-6.75 (2H, m), 7.15-7.5 (3H, m), 7.5-7.8 (3H, m), 7.96 (1H, d, J=7Hz), 11.95 (1H, br), 12.41 (1H, br)

NMR (17) (DMSO-d_6) δppm; 1.45-1.9 (2H, m), 2.0-2.35 (4H, m), 2.55-2.95 (6H, m), 2.95-3.25 (1H, m), 3.3-3.95 (12H, m), 4.0-4.35 (3H, m), 4.4-4.65 (1H, m), 6.4-6.75 (2H, m), 7.25 (1H, d, J=15Hz), 7.2-7.5 (2H, m), 7.55 (1H, d, J=15Hz), 7.61 (1H, d, J=9.5Hz), 7.71 (1H, d, J=7.5Hz), 7.96 (1H, d, J=7Hz), 11.9-12.8 (2H,m)

NMR (18) (DMSO-d_6) δppm; 1.16 (3H, t, J=7.5Hz), 1.9-2.2 (2H, m), 2.48 (3H, s), 2.62 (2H, q, J=7.5Hz), 2.82 (3H, d, J=4.5Hz), 3.0-3.8 (5H, m), 3.84 (3H, s), 3.9-4.3 (3H, m), 5.16 (2H, s), 6.71 (1H, s), 7.22 (1H, d, J=15Hz), 7.25-7.35 (1H, m), 7.4-7.5 (1H, m), 7.51 (1H, s), 7.66 (1H, dd, J=5.5Hz, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 9.55 (1H, br), 11.7 (1H,br)

NMR (19) (DMSO-d_6) δppm; 1.15 (3H, t, J=7.5Hz), 1.35-1.7 (2H, m), 1.9-

2.1 (2H, m), 2.36 (3H, s), 2.5-2.7 (3H, m), 2.73 (3H, s), 2.75 (3H, s), 3.0-3.2 (1H, m), 3.3-3.55 (1H, m), 3.84 (3H, s), 4.05-4.25 (1H, m), 4.45-4.65 (1H, m), 5.16 (2H, s), 6.71 (1H, s), 7.26 (1H, d, J=15Hz), 7.25-7.35 (1H, m), 7.4-7.5 (1H, m), 7.50 (1H, s), 7.58 (1H, d, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 9.58 (1H, br)

NMR (20) (DMSO-d_6) δppm; 0.90 (3H, t, J=7.5Hz), 1.57 (2H, tq, J=7.5Hz, J=8Hz), 2.35 (3H, s), 2.57 (2H, t, J=8Hz), 2.81 (3H, d, J=3.5Hz), 2.9-3.25 (3H, m), 3.3-3.7 (3H, m), 3.83 (3H, s), 4.15-4.4 (1H, m), 4.4-4.65 (1H, m), 5.16 (2H, s), 6.70 (1H, s), 7.28 (1H, d, J=15Hz), 7.25-7.4 (1H, m), 7.4-7.5 (1H, m), 7.49 (1H, s), 7.66 (1H, d, J=15Hz), 7.77 (1H, d, J=8Hz), 7.98 (1H, d, J=7.5Hz), 9.85 (1H, br), 12.6 (1H, br)

NMR (21) (DMSO-d_6) δppm; 0.89 (3H, t, 7.5Hz), 1.4-1.9 (4H, m), 2.0-2.4 (4H, m), 2.5-2.85 (6H, m), 3.0-4.05 (10H, m), 3.84 (3H, s), 4.05-4.3 (1H, m), 4.45-4.7 (1H, m), 5.17 (2H, s), 6.71 (1H, s), 7.15-7.35 (2H, m), 7.35-7.5 (1H, m), 7.48 (1H, s), 7.58 (1H, d, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.1-13.2 (2H, m)

NMR (22) (DMSO-d_6) δppm; 0.90 (3H, t, J=7.5Hz), 1.4-1.8 (4H, m), 1.95 - 2.25 (2H, m), 2.57 (2H, t, J=8Hz), 2.6-2.9 (1H, m), 2.81 (3H, s), 2.95-4.0 (10H, m), 3.84 (3H, s), 4.05-4.3 (1H, m), 4.4-4.65 (1H, m), 5.16 (2H, s), 6.70 (1H, s), 7.26 (1H, d, J=15Hz), 7.25-7.35 (1H, m), 7.35-7.5 (1H, m), 7.48 (1H, s), 7.58 (1H, d, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.4-13.0 (3H, m)

NMR (23) (DMSO-d_6) δppm; 0.90 (3H, t, J=7.5Hz), 1.57 (2H, tq, J=7.5Hz, J=8Hz), 2.57 (2H, t, J=8Hz), 2.65-4.4 (17H, m), 2.79 (3H, s), 3.84 (3H, s), 5.18 (2H, s), 6.71 (1H, s), 7.15-7.5 (3H, m), 7.48 (1H, s), 7.5-7.8 (2H, m), 7.98 (1H, d,

J=7Hz), 11.0-13.0 (3H, m)

NMR (24) (DMSO-d_6) δppm; 1.11 (3H, t, J=7.4Hz), 2.53-4.17 (16H, m), 2.59 (2H, q, J=7.4Hz), 2.79 (3H, s), 3.84 (3H, s), 4.17-4.40 (1H, m), 5.20 (2H, s), 6.73 (1H, s), 7.18-7.38 (2H, m), 7.38-7.54 (2H, m), 7.54-7.74 (1H, m), 7.74-7.81 (1H, m), 7.92-8.05 (1H, m), 11.32-13.11 (3H, m)

NMR (25) (DMSO-d_6) δppm; 2.35 (3H, s), 2.80 (3H, d, J=3.5Hz), 2.85-3.6 (6H, m), 3.85 (3H, s), 4.04 (2H, br), 4.2-4.6 (2H, m), 5.0-5.25 (4H, m), 5.81-6.1 (1H, m), 6.74 (1H, s), 7.28 (1H, d, J=15Hz), 7.25-7.55 (2H, m), 7.48(1H, s), 7.65 (1H, d, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 9.99 (1H, br), 12.6 (1H, br)

NMR (26) (DMSO-d_6) δppm; 1.65 (2H, br), 2.0-2.4 (4H, m), 2.55-2.95 (4H, m), 3.0-3.25 (1H, m), 3.25-4.05 (14H, m), 4.05-4.3 (1H, m), 4.45-4.7 (1H, m), 4.95-5.3 (4H, m), 5.85-6.1 (1H, m), 6.75 (1H, s), 7.15-7.7 (5H, m), 7.77 (1H, d, J=8Hz), 7.98 (1H, d, J=7.5Hz), 11.1-13.0 (3H, m)

NMR (27) (DMSO-d_6) δppm; 1.4-1.85 (2H, m), 1.95-2.3 (2H, m), 2.55-2.95 (4H, m), 2.95-3.2 (1H, m), 3.2-3.95 (11H, m), 5.86 (3H, s), 4.1-4.3 (1H, m), 4.45-4.7 (1H, m), 4.95-5.25 (4H, m), 5.86-6.1 (1H, m), 6.74 (1H, s), 7.26 (1H, d, J=15Hz), 7.25-7.55 (3H, m), 7.56 (1H, d, J=15Hz), 7.77 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7Hz), 11.3-13.2 (3H, m)

NMR (28) (DMSO-d_6) δppm; 2.55-4.45 (25H, m), 4.9-5.3 (4H, m), 5.85-6.1 (1H, m), 6.75 (1H, s), 7.15-7.85 (6H, m), 7.98 (1H, d, J=7Hz), 11.0-13.3 (3H, m)

NMR (29) (DMSO-d_6) δppm; 1.32 (3H, t, J=7Hz), 2.33 (3H, s), 2.80 (3H,s), 2.9-3.2 (3H, m), 3.3-3.5 (3H, m), 3.81 (3H, s), 4.03 (2H, q, J=7Hz), 4.2-4.65 (2H, m), 5.15 (2H, s), 6.83 (1H, s), 7.2-7.4 (3H, m), 7.44 (1H, t, J=8Hz), 7.69 (1H, d, J=15Hz), 7.77 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 9.83 (1H, br), 12.60 (1H, br)

NMR (30) (DMSO-d_6) δppm; 1.32 (3H, t, J=7Hz), 1.4-1.9 (2H, m), 2.05-2.4 (4H, m), 2.6-3.9 (4H, m), 3.05-3.95 (13H, m), 4.03 (2H, q, J=7Hz), 4.1-4.3 (1H, m), 4.5-4.7 (1H, m), 5.17 (2H, s), 6.83 (1H, s), 7.2-7.4 (3H, m), 7.44 (1H, t, J=8Hz), 7.60 (1H, d, J=15.5Hz), 7.76 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 11.25-12.2 (2H, m)

NMR (31) (DMSO-d_6) δppm; 1.32 (3H, t, J=7Hz), 2.55-4.5 (19H, m), 2.80 (3H, s), 3.82 (3H, s), 5.17 (2H, s), 6.84 (1H, s), 7.2-7.4 (3H, m), 7.44 (1H, t, J=8Hz), 7.64 (1H, d, J=15.5Hz), 7.76 (1H, d, J=8Hz), 7.98 (1H, d, J=8Hz), 11.5-12.5 (2H, m)

NMR (32) (DMSO-d_6) δppm; 2.32 (3H, s), 2.81 (3H, s), 3.4-3.7 (4H, m), 3.25-3.6 (2H, m), 3.86 (3H, s), 4.15-4.65 (2H, m), 5.26 (2H, s), 6.89 (1H, s), 7.32 (1H, d, J=15Hz), 7.32 (1H, t, J=7.5Hz), 7.45 (1H, t, J=8Hz), 7.61 (1H, d, J=15Hz), 7.77 (1H, d, J=8Hz), 7.83 (1H,s), 7.98 (1H, d, J=7.5Hz), 9.78 (1H, br), 12.65 (1H, br)

NMR (33) (DMSO-d_6) δppm; 1.4-1.85 (2H, m), 2.1-2.4 (4H, m), 2.6-3.9 (4H, m), 3.05-4.5 (14H, m), 4.5-4.65 (1H, m), 5.27 (2H, s), 6.89 (1H, s), 7.2-7.4 (2H, m), 7.4-7.6 (2H, m), 7.77 (1H, d, J=8Hz), 7.81 (1H, s), 7.98 (1H, d, J=8Hz), 11.1-12.1 (2H, m)

NMR (34) (DMSO-d_6) δppm; 2.35(s, 6H), 2.82 (s, 3H), 2.92-3.27 (m, 9H), 3.30-3.59 (m, 3H), 4.18 (br, 1H), 4.19-4.34 (m, 1H), 4.47-4.65 (m, 1H), 5.24 (s, 2H), 7.33 (t, J=7.6Hz, 2H), 7.44 (d, J=7.3Hz, 1H), 7.46 (d, J=15.1Hz, 1H), 7.78 (d, J=8.0Hz, 1H), 7.84 (d, J=15.1Hz, 1H), 7.96-8.15 (m, 3H), 9.82 (br, 1H), 12.66 (br, 1H)

NMR (35) (DMSO-d_6) δppm; 1.42-1.88 (m, 2H), 1.93-2.39(m, 4H), 2.59-

2.85 (m, 4H), 3.13 (s, 6H), 3.26-3.96 (m, 10H), 4.05-4.28 (m, 1H), 4.51-4.68 (m, 1H), 5.26 (s, 2H), 7.29-7.35 (m, 2H), 7.42-7.48 (m, 2H), 7.74-7.80 (m, 2H), 7.96-8.04 (m, 2H), 8.19 (br, 1H), 11.35-12.13 (m, 2H)

NMR (36) (DMSO-d_6) δppm; 4.61-4.78 (2H, m), 5.05 (2H, s), 5.18-5.50 (2H, m), 5.91-6.17 (1H, m), 6.46 (1H, d, J=15.5Hz), 6.62-6.78 (1H, m), 6.78-6.88 (1H, m), 7.28-7.39 (1H, m), 7.39-7.52 (1H, m), 7.54-7.81 (2H, m), 7.71 (1H, d, J=15.5Hz), 7.92-8.05 (1H, m), 12.72 (2H, brs)

NMR (37) (DMSO-d_6) δppm; 4.97 (2H, s), 6.40-6.58 (2H, m), 6.91 (1H, dd, J=2.4Hz, J=8.8Hz), 7.00-7.22 (3H, m), 7.22-7.51 (4H, m), 7.61-7.89 (3H, m), 7.89-8.04 (1H, m), 12.75 (2H, brs)

NMR (38) (DMSO-d_6) δppm; 1.12 (3H, t, J=7.4Hz), 2.60 (2H, q, J=7.4Hz), 3.85 (3H, s), 5.15 (2H, s), 6.46 (1H, d, J=15.5Hz), 6.71 (1H, s), 7.26-7.39 (1H, m), 7.39-7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, d, J=15.5Hz), 7.72-7.81 (1H, m), 7.91-8.03 (1H, m), 12.75 (2H, brs)

NMR (39) (DMSO-d_6) δppm; 2.19 (3H, s), 3.64 (3H, s), 5.07 (2H, s), 6.54 (1H, d, J=15.6Hz), 6.85 (1H, d, J=8.7Hz), 7.25-7.40 (1H, m), 7.40-7.51 (1H, m), 7.54 (1H, d, J=8.8Hz), 7.68 (1H, d, J=15.6Hz), 7.76 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7.5Hz), 12.41-13.16 (2H, m)

NMR (40) (DMSO-d_6) δppm; 2.16 (3H, s), 3.88 (3H, s), 4.64 (2H, s), 6.52 (1H, d, J=15.6Hz), 6.95 (1H, d, J=8.8Hz), 7.21-7.38 (1H, m), 7.38-7.51 (1H, m), 7.55-7.80 (3H, m), 7.98 (1H, d, J=7.1Hz)

NMR (41) (DMSO-d_6) δppm; 0.91 (3H, t, J=7.3Hz), 1.20-1.65 (4H, m), 2.54-2.78 (2H, m), 3.63 (3H, s), 5.07 (2H, s), 6.58 (1H, d, J=15.6Hz), 6.84 (1H, d, J=8.7Hz), 7.21-7.39 (1H, m), 7.39-7.51 (1H, m), 7.55 (1H, d, J=8.7Hz), 7.67 (1H, d,

J=15.6Hz), 7.76 (1H, d, J=7.8Hz), 7.97 (1H, d, J=7.8Hz), 12.05-13.51 (2H, m)

NMR (42) (DMSO-d_6) δppm; 2.41 (3H, s), 5.10 (2H, s), 6.56 (1H, d, J=15.5Hz), 6.90 (1H, dd, J=8.8Hz, J=2.2Hz), 6.98 (1H, d, J=2.2Hz), 7.32 (1H, t, J=7.2Hz), 7.45 (1H, t, J=7.2Hz), 7.65-7.85 (2H, m), 7.99 (1H, d, J=7.7Hz), 8.05 (1H, d, J=8.8Hz), 12.06-13.45 (2H, m)

NMR (43) (DMSO-d_6) δppm; 1.17 (3H, t, J=7.5Hz), 2.70 (2H, q, J=7.5Hz), 3.65 (3H, s), 5.09 (2H, s), 6.57 (1H, d, J=15.6Hz), 6.85 (1H, d, J=8.9Hz), 7.30 (1H, dt, J=1.2Hz, J=7.1Hz), 7.43 (1H, dt, J=1.2Hz, J=7.1Hz), 7.56 (1H, d, J=8.9Hz), 7.67 (1H, d, J=15.6Hz), 7.76 (1H, d, J=7.1Hz), 7.97 (1H, d, J=7.1Hz), 12.51-13.12 (2H, m)

NMR (44) (DMSO-d_6) δppm; 3.79 (3H, s), 3.83 (3H, s), 5.12 (2H, s), 6.51 (1H, d, J=15.5Hz), 6.84 (1H, s), 7.15-7.54 (3H, m with 1H s at 7.26), 7.61-7.86 (2H, m with 1H, d at 7.76 J=15.5Hz), 7.99 (1H, d, J=7.1Hz), 12.20-13.25 (2H, m)

NMR (45) (DMSO-d_6) δppm; 2.19 (3H, s), 3.85 (3H, s), 5.14 (2H, s), 6.49 (1H, d, J=15.5Hz), 6.70 (1H, s), 7.20-7.56 (3H, m, with 1H s at 7.52), 7.60-7.82 (2H, m, with 1H d at 7.71 J=15.5Hz), 7.98 (1H, d, J=7.0Hz), 12.41-13.17(2H, m)

NMR (46) (DMSO-d_6) δppm; 1.19 (6H, d, J=6.9Hz), 3.10-3.42 (1H, m), 3.86 (3H, s), 5.16 (2H, s), 6.50 (1H, d, J=15.5Hz), 6.70 (1H, s), 7.21-7.60 (3H, m with 1H s at 7.55), 7.65-7.82 (2H, m with 1H d at 7.73 J=15.5Hz), 7.89-8.08 (1H, m), 12[illegible]-13.12 (2H, m)

NMR (47) (DMSO-d_6) δppm; 0.68-0.92 (3H, m), 1.08-1.64 (8H, m), 2.38-2.68 (2H, m), 3.85 (3H, s), 5.14 (2H, s), 6.49 (1H, d, J=15.5Hz), 6.71 (1H, s), 7.20-7.57 (3H, m), 7.62-7.85 (2H, m with 1H d at 7.72 J=15.5Hz), 7.88-8.05 (1H, m), 12.45-13.12 (2H, m)

NMR (48) (DMSO-d_6) δppm; 3.17 (s, 6H), 5.28 (s, 2H), 6.71 (d, J=15.5Hz, 1H), 7.29-7.49 (m, 3H), 7.78 (d, J=8.0Hz, 1H), 7.91-8.06 (m, 2H), 8.09 (d, J=8.4Hz, 1H), 8.25 (s, 1H)

NMR (49) (DMSO-d_6) δppm; 3.87 (s, 3H), 4.75 (d, J=5Hz, 2H), 4.77 (s, 2H), 6.50 (d, J=15.5Hz, 1H), 6.72 (dd, J=2.2Hz J=8.6Hz, 1H), 6.78 (d, J=2.2Hz, 1H), 7.33-7.57 (m, 2H), 7.66 (d, J=8.6Hz, 1H), 7.69 (d, J=15.5Hz, 1H), 7.94 (d, J=7.4Hz, 1H), 8.05 (d, J=6.9Hz, 1H), 9.18 (t, J=5.1Hz, 1H), 12.99 (br, 1H)

PHARMACOLOGICAL EXPERIMENTS

(1) Protein kinase C (PKC) inhibitory activity

Method for determining PKC activity:

The purification of PKC using rat's brain soluble fractions was carried out by a method of Kikkawa et al. (cf. Ushio Kikkawa, Yoshimi Takai, Ryoji Minakuchi, Sinichi Inohara and Yasutomi Nishizuka: The Journal of Biological Chemistry, vol. 257, No. 22, pp. 13341-13348 (1982)). PKC activity was determined by the transfer of radio activity from the [γ-^{32}P] adenosine triphosphate (ATP) to H1 histone derived from calf thymus in the presence of 20 mM Tris-HCl buffer (pH 7.5), H1 histone derived from calf thymus (200 μg/ml), 10 μM [γ-^{32}P]ATP, 5 mM magnesium acetate, 8 μg/ml phosphatidyl serine, 2 μg/ml diacylglycerol and 0.3 mM Ca^{2+}. The test compound was dissolved in dimethylformamide, and the test compound solution was added to the assay system so that the final concentration thereof was adjusted to 0.8 %. The reaction mixture was incubated at 30°C for 30 minutes, and the reaction was quenched with 25 % trichloroacetic acid. The acid-insoluble protein was collected on a nitrocellulose membrane by suction filtration. The radio activity

of ^{32}P was determined by scintillation counter. The PKC inhibitory activity of the test compounds was expressed by IC_{50}, which is a concentration of the test compound to be required to reduce the PKC activity by 50 %. The results are shown in Table 196.

Results:

Table 196

Test compound	PKC inhibitory activity (IC_{50}, μM)
The compound of Example 71	0.8
The compound of Example 88	0.1
The compound of Example 89	0.3
The compound of Example 100	0.3
The compound of Example 160	0.6
The compound of Example 182	0.08
The compound of Example 192	0.8
The compound of Example 197	0.3

(2) Mouse collagen arthritis

Bovine II-type collagen (provided by Collagen Gijyutsu Kensyukai) (0.1 %) was emulsified with Complete Fleund's adjuvant (CFA) (50 %) (manufactured by DIFCO, Ltd.), and the emulsion thus obtained was injected intracutaneously to mice at the tail (primary sensitization). Three weeks later, bovine II-type collagen (0.1 %) was injected intraperitoneally again to the mice

(secondary sensitization). Three weeks later, the swelling of limbs of the mice was observed, and evaluated by four-degree as 0 to 3 each limb. The degree (0 to 3) each limb was added, and the results were used a score of the arthritis. That is, the maximum degree is 12 (degree 3 X 4 limb). The test compound was administered orally to the mice once a day, which started after two weeks from the primary sensitization.

In the mice treated with the compound of Example 182 at a dose of 30 to 50 mg/kg, the score of arthritis was significantly reduced in comparison with the control mice.

In the mice treated with the compounds of Example 160, 192 or 197 at a dose of 50 mg/kg, the score of arthritis was significantly reduced in comparison with the control mice.

(3) Mouse cGVHD (chromic Graft-versus-host disease model)

Female mice (DBA/2NCrj) were subjected to an operation of cervical vertebra dislocation, and the spleen was taken out to give the spleen cells preparation. The preparation were adjusted to 37.5 x 10^7 cells/ml, and administered to the BDF1 female mice on the tail vein at a dose of 200 μl per a mouse. Two weeks later, the blood was collected in the absence of heparin, and anti-DNA antibody therein was determined by ELISA.

The compound of Example 182 was administered orally to the mice at a dose of 30 to 50 mg/kg once a day for two weeks, and the effect of the test compound on cGVHD was determined.

The amount of anti-DNA antibody in the blood was determined with OD_{405}. The amounts of anti-DNA antibody were 0.348±0.111 (mean±s.e.) in

the control group, 0.255±0.062 (mean±s.e.) in the group treated with the compound of Example 182 at a dose of 30 mg/kg, and 0.094±0.026 (mean±s.e.) in the group treated with the compound of Example 182 at a dose of 50 mg/kg. From the results, it was proved that the compound of Example 182 reduced the anti-DNA antibody in the blood dose-dependently, compared with the control group.

Further, the compound of Example 100 was also administered orally to the mice at 30 mg/kg once a day for two weeks, and the effect of the compound on cGVHD was also determined.

The amount of anti-DNA antibody in the blood was determined with OD_{405}. The amounts of anti-DNA antibody were 0.258±0.084 (mean±s.e.) in the control group, and 0.177±0.061 (mean±s.e.) in the group treated with the compound of Example 100 at a dose of 30 mg/kg. From the results, it was proved that the compound of Example 100 reduced the anti-DNA antibody in the blood, compared with the control group.

(4) Rat kidney ischemic re-perfusion model

The right kidney of a SD male rat was taken out, and the left kidney artery was clumped, and then, re-perfused to give a kidney ischemic re-perfusion model. The effect of the compounds of Examples 71, 89 and 100 on the kidney ischemic re-perfusion model was estimated.

The compound of Example 71 was administered intravenously to the rat at a dose of 3 mg/kg 5 minutes before the ischemic. Twenty-four hours later, the blood was collected from the tail vein, and the amounts of creatine and urea nitrogen were determined. The amount of creatine in the blood was 2.19±0.21 (mean±s.e.) in the control group; 1.4±0.11 (mean±s.e.) in the group treated with

the compound of Example 71, and the amount of urea nitrogen in the blood was 78.8±5.6 (mean±s.e.) in the control group, and 54.1±5.0 (mean±s.e.) in the group treated with the compound of Example 71. That is, the compound of Example 71 significantly reduced the amounts of both of creatine and urea nitrogen, compared with the control group.

The compound of Example 89 was administered intravenously to the rat at a dose of 3 mg/kg 5 minutes before the ischemic and the re-perfusion. Forty-eight hours later, the blood was collected from the tail vein, and the amounts of creatine and urea nitrogen were determined. The amount of creatine in the blood was 4.31±0.53 (mean±s.e.) in the control group; 2.34±0.46 (mean±s.e.) in the group treated with the compound of Example 89, and the amount of urea nitrogen in the blood was 155.1±15.4 (mean±s.e.) in the control group, and 99.1±16.0 (mean±s.e.) in the group treated with the compound of Example 89. That is, the compound of Example 89 significantly reduced the amounts of both of creatine and urea nitrogen, compared with the control group.

The compound of Example 100 was administered orally to the rat at a dose of 30 mg/kg one hour before the ischemic. Forty-eight hours later, the blood was collected from the tail vein, and the amounts of creatine and urea nitrogen were determined. The amount of creatine in the blood was 2.48±0.59 (mean±s.e.) in the control group; 1.53±0.20 (mean±s.e.) in the group treated with the compound of Example 100, and the amount of urea nitrogen in the blood was 91.3±20.1 (mean±s.e.) in the control group, and 63.1±10.3 (mean±s.e.) in the group treated with the compound of Example 100. Thus, it is proved that the compound of Example 100 reduced the amounts of both of creatine and urea nitrogen, compared with the control group.

(5) Phorbol ester (TPA)-induced mouse auricle edema, acanthosis model

A 200 μg/ml phorbol ester (TPA) (10 μl) was applied to the one side to the ear of a female mouse (ICR). Twenty-four hours later, the thickness of the auricle of the mouse was determined with using a dialthickness gage, and the increase in the thickness of auricle was calculated. A test compound was dissolved in acetone, and the solution of a test compound was applied to the both sides of the ear 30 minutes before the application of TPA.

The compound of Example 88 was applied to the ear at a dose of 20 μl of 0.3 % or 1 % solution. The increase in the thickness of auricle in the control group is 215±40 μm (mean±s.e.) after 24 hours, while 87±53 μm (mean±s.e.) in the group treated with the compound of Example 88 in 0.3 %, and 67±23 μm (mean±s.e.) in the group treated with the compound of Example 88 in 1 %. Thus, the compound of Example 88 significantly reduced the increase in auricle thickness, compared with the control group.

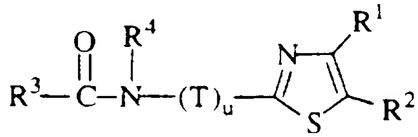
(6) Mouse atopic dermatitis model:

1 % Trinitrobenzene (TNCB), (10 μl) was applied to each side of the ear of female mice (Balb/c), once every two days for 24 days. Twenty-four days later, the mice were grouped, and the auricle thickness of the mouse was determined by using a dial thickness gage, and the increase in the thickness of auricle was calculated. The compounds of Examples 88 and 89 were dissolved in acetone in a concentration of 1 %. The compound of Example 182 was dissolved in a mixture of acetone:methanol in a concentration of 0.75 %. Twenty-four days after the beginning of the experiment, the solution of a test compound was applied to each side of the ear 30 minutes before and after the application of TNCB, once a day for two weeks. The compound of Example 88

inhibited the increase in the auricle thickness by 25 to 30 %, and the compounds of Examples 89 and 182 inhibited the increase in the auricle thickness by about 25 %. Thus, it is proved that the compounds of the present invention is useful in the treatment of acanthosis induced by the application of TNCB.

CLAIMS

1. A thiazole compound of the formula:

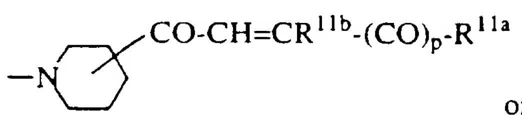


wherein T is a lower alkylene;

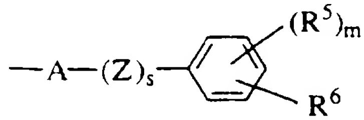
u is 0 or 1;

R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl, or both combine to form a group: $-(CH_2)_n-$ (n is 4 or 5) or to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom;

R^3 is a group of the formula:



or



wherein R^{11b}, p, R^{11a} are defined hereinafter; A is a lower alkylene; Z is O or S; s is 0 or 1; m is 1 or 2;

R^4 is a hydrogen atom or a lower alkanoyloxy-lower alkyl;

R^5s are the same or different and are each a member selected from (a) a hydrogen atom, (b) an alkyl having optionally a hydroxy substituent, (c) a halogen atom, (d) a group of the formula: $-(O)_t-A-(CO)_\ell-NR^7R^8$ (wherein t is 0 or 1, A is a lower alkylene, l is 0 or 1, and R^7 and R^8 are the same or different and

are each a hydrogen atom or a lower alkyl, or both combine together with the nitrogen atom to which they bond to form a 5- to 7-membered saturated heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group being optionally substituted by a member selected from a group of the formula: $-(A)_l-NR^9R^{10}$ (wherein A and l are as defined above, and R^9 and R^{10} are the same or different and are each a hydrogen atom or a lower alkyl, or both combine together with the nitrogen atom to which they bond to form a 5- to 7-membered saturated heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group having optionally a lower alkyl substituent), a lower alkyl having optionally a hydroxy substituent, a hydroxy group, and a lower alkanoyl), (e) a lower alkoxycarbonyl-lower alkyl, (f) a lower alkanoyloxy-lower alkyl, (g) a lower alkoxy having optionally a halogen substituent, (h) a halogen-substituted lower alkyl, (i) a carboxyl-substituted lower alkyl, (j) a lower alkoxycarbonyl, (k) a lower alkenyloxy, (l) a phenyl-lower alkoxy, (m) a cycloalkyloxy, (n) a phenyl, (o) a phenyloxy, (p) a hydroxy, (q) a lower alkylthio, (r) a lower alkenyl, or (s) an amino having optionally a lower alkyl substituent;

R^6 is a group of the formula:

(1) $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ or (2) $-CO-C\equiv C-COR^{14}$;

p is 0 or 1;

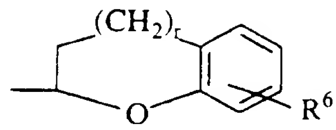
R^{11b} is a hydrogen atom or a lower alkyl;

R^{11a} is a hydroxy, a lower alkoxy, or a 5- to 10-membered, monocyclic or dicyclic, saturated or unsaturated heterocyclic group which contains 1 to 4

hetero atoms selected from a nitrogen, oxygen or sulfur atom as a ring member, said heterocyclic group having optionally 1 to 3 substituents selected from the group consisting of (i) a lower alkyl, (ii) a group of the formula: $-(B)_l-NR^{12}R^{13}$ (wherein l is as defined above, B is -CO-A- (A is as defined above), a carbonyl, or a lower alkylene, and R^{12} and R^{13} are the same or different and are each a hydrogen atom, a lower alkyl, or a lower alkyl substituted by an amino having optionally a lower alkyl substituent, or both combine together with the nitrogen atom to which they bond to form a 5- to 12-membered saturated, monocyclic, dicyclic or spirocyclic heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group having optionally a substituent selected from a lower alkyl, a lower alkoxycarbonyl, a lower alkoxy-substituted lower alkyl, an amino having optionally a lower alkyl substituent, and a hydroxy-substituted lower alkyl), (iii) a lower alkoxycarbonyl, (iv) a hydroxy-substituted lower alkyl, (v) a pyridyl being optionally substituted by a lower alkyl having optionally a halogen substituent on the pyridine ring, (vi) a halogen-substituted lower alkyl, (vii) a lower alkoxy, (viii) a cycloalkyl, (ix) a hydroxy, (x) a tetrahydropyranyloxy-substituted lower alkyl, (xi) a pyrimidyl, (xii) a lower alkoxy-substituted lower alkyl, (xiii) a carboxyl, (xiv) a phenyl-lower alkoxy, (xv) a phenyl-lower alkyl having optionally a lower alkylene-dioxy on the phenyl ring, (xvi) a lower alkanoyloxy, and (xvii) a piperidinyl having optionally a lower alkyl substituent on the piperidine ring;

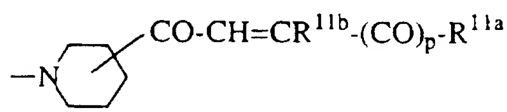
R^{14} is a hydroxy or a lower alkoxy; and

when m is 1, the groups A and R^5 may combine to form a group of the formula:



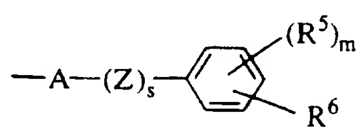
(wherein R^6 is as defined above, and r is 0, 1 or 2), or when m is 2, two R^5 groups may combine to form a lower alkylenedioxy, a lower alkylene, or a group of the formula: $-(CH_2)_2-CONH-$, or the groups R^5 and R^6 may combine to form a group of the formula: $-CO-CH(R^{28})-CH(R^{28'})-W-$ (wherein R^{28} and $R^{28'}$ are a hydrogen atom or a carboxyl group, provided that both R^{28} and R^{28} are not simultaneously a carboxyl group, and W is $-N(R^{29a})-$ or $-\overset{+}{N}(R^{29b})-R^{29b} \cdot X^-$ (wherein R^{29a} is a hydrogen atom or a lower alkyl, R^{29b} is a lower alkyl, and X is as defined above)), or a salt thereof.

2. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl; and R^3 is a group of the formula:



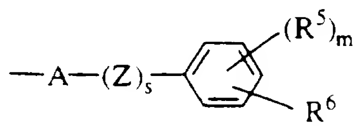
(wherein R^{11b}, R^{11a} and p are as defined in claim 1), or a salt thereof.

3. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl; and R^3 is a group of the formula:



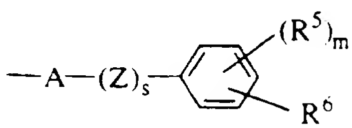
(wherein A, R^5, R^6 and m are as defined in claim 1, and s is 0), or a salt thereof.

4. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl; and R^3 is a group of the formula:



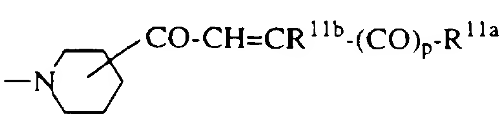
(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is O), or a salt thereof.

5. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl; and R^3 is a group of the formula:



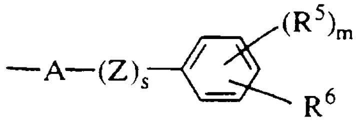
(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is S), or a salt thereof.

6. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4); and R^3 is a group of the formula:



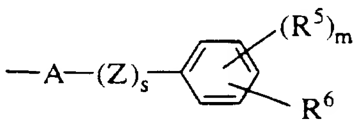
(wherein R^{11b}, R^{11a} and p are as defined in claim 1), or a salt thereof.

7. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4); and R^3 is a group of the formula:



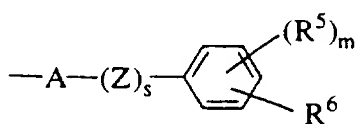
(wherein A, R^5, R^6 and m are as defined in claim 1, and s is 0), or a salt thereof.

8. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4); and R^3 is a group of the formula:



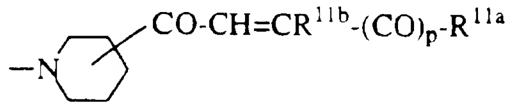
(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is O), or a salt thereof.

9. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 4); and R^3 is a group of the formula:



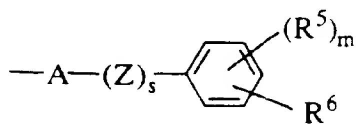
(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is S), or a salt thereof.

10. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5); and R^3 is a group of the formula:



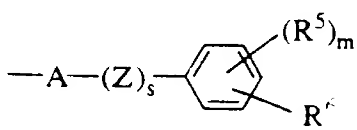
(wherein R^{11b}, R^{11a} and p are as defined in claim 1), or a salt thereof.

11. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5); and R^3 is a group of the formula:



(wherein A, R^5, R^6 and m are as defined in claim 1, and s is 0), or a salt thereof.

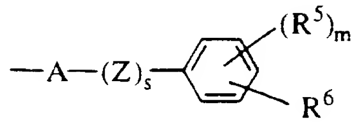
12. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5); and R^3 is a group of the formula:



(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is O), or a salt thereof.

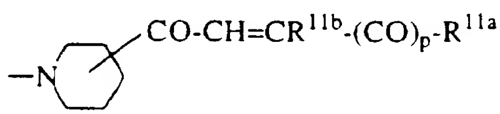
13. The thiazole compound according to claim 1, wherein u is 0; R^1

and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5); and R^3 is a group of the formula:



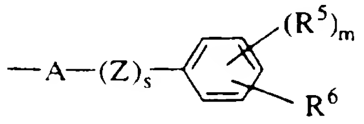
(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is S), or a salt thereof.

14. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom; and R^3 is a group of the formula:



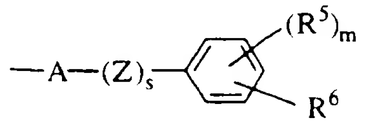
(wherein R^{11b}, R^{11a} and p are as defined in claim 1), or a salt thereof.

15. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom; and R^3 is a group of the formula:



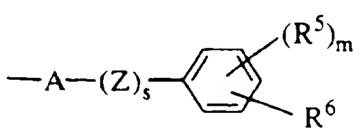
(wherein A, R^5, R^6 and m are as defined in claim 1, and s is 0), or a salt thereof.

16. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom; and R^3 is a group of the formula:



(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is O), or a salt thereof.

17. The thiazole compound according to claim 1, wherein u is 0; R^1 and R^2 combine to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom; and R^3 is a group of the formula:



(wherein A, R^5, R^6 and m are as defined in claim 1, s is 1, and Z is S), or a salt

thereof.

18. The thiazole compound according to claim 4, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} and p are as defined in claim 1, and R^{11a} is a hydroxy or a lower alkoxy, or a salt thereof.

19. The thiazole compound according to claim 4, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} is as defined in claim 1, p is 1, and R^{11a} is a 5- to 10-membered, monocyclic or dicyclic, saturated or unsaturated heterocyclic group which contains 1 to 4 hetero atoms selected from a nitrogen, oxygen or sulfur atom as a ring member, said heterocyclic group having optionally 1 to 3 substituents selected from the group consisting of (i) a lower alkyl, (ii) a group of the formula: $-(B)_\ell-NR^{12}R^{13}$ (wherein ℓ is as defined above, B is -CO-A- (A is as defined above), a carbonyl, or a lower alkylene, and R^{12} and R^{13} are the same or different and are each a hydrogen atom, a lower alkyl, or a lower alkyl substituted by an amino having optionally a lower alkyl substituent, or both combine together with the nitrogen atom to which they bond to form a 5- to 12-membered saturated, monocyclic, dicyclic or spirocyclic heterocyclic group which may be intervened with a nitrogen or oxygen atom, said heterocyclic group having optionally a substituent selected from a lower alkyl, a lower alkoxycarbonyl, a lower alkoxy-substituted lower alkyl, an amino having optionally a lower alkyl substituent, and a hydroxy-substituted lower alkyl), (iii) a lower alkoxycarbonyl, (iv) a hydroxy-substituted lower alkyl, (v) a pyridyl being optionally substituted by a lower alkyl having optionally a halogen substituent on the pyridine ring, (vi) a halogen-substituted lower alkyl,

(vii) a lower alkoxy, (viii) a cycloalkyl, (ix) a hydroxy, (x) a tetrahydropyranyl-oxy-substituted lower alkyl, (xi) a pyrimidyl, (xii) a lower alkoxy-substituted lower alkyl, (xiii) a carboxyl, (xiv) a phenyl-lower alkoxy, (xv) a phenyl-lower alkyl having optionally a lower alkylenedioxy on the phenyl ring, (xvi) a lower alkanoyloxy, and (xvii) a piperidinyl having optionally a lower alkyl substituent on the piperidine ring, or a salt thereof.

20. The thiazole compound according to claim 4, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} is as defined in claim 1, p is 0, and R^{11a} is as defined in claim 19, or a salt thereof.

21. The thiazole compound according to claim 4, wherein R^6 is a group of the formula: $-CO-C{\equiv}C-COR^{14}$ wherein R^{14} is as defined in claim 1, or a salt thereof.

22. The thiazole compound according to claim 16, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} and p are as defined in claim 1, and R^{11a} is a hydroxy or a lower alkoxy, or a salt thereof.

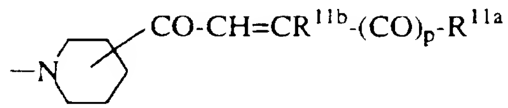
23. The thiazole compound according to claim 16, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} is as defined in claim 1, p is 1, and R^{11a} is as defined in claim 19, or a salt thereof.

24. The thiazole compound according to claim 16, wherein R^6 is a group of the formula: $-CO-CH=CR^{11b}-(CO)_p-R^{11a}$ wherein R^{11b} is as defined in claim 1, p is 0, and R^{11a} is as defined in claim 19, or a salt thereof.

25. The thiazole compound according to claim 16, wherein R^6 is a

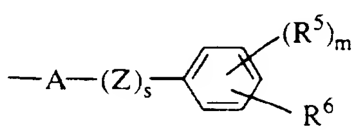
group of the formula: -CO-C≡C-COR^{14} wherein R^{14} is as defined in claim 1, or a salt thereof.

26. The thiazole compound according to claim 1, wherein u is 1; and R^3 is a group of the formula:



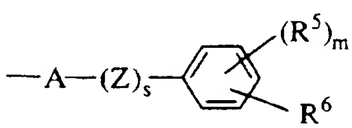
(wherein R^{11b}, R^{11a} and p are as defined in claim 1), or a salt thereof.

27. The thiazole compound according to claim 1, wherein u is 1; R^1 and R^2 are the same or different and are each a hydrogen atom or a lower alkyl; and R^3 is a group of the formula:



(wherein A, Z, s, R^5, R^6 and m are as defined in claim 1), or a salt thereof.

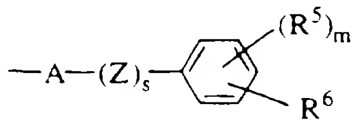
28. The thiazole compound according to claim 1, wherein u is 1; R^1 and R^2 combine to form a group: -(CH$_2$)$_n$- (n is 4); and R^3 is a group of the formula:



(wherein A, Z, s, R^5, R^6 and m are as defined in claim 1), or a salt thereof.

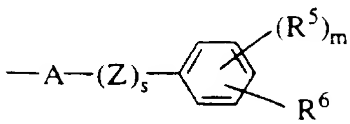
29. The thiazole compound according to claim 1, wherein u is 1; R^1

and R^2 combine to form a group: $-(CH_2)_n-$ (n is 5); and R^3 is a group of the formula:



(wherein A, Z, s, R^5, R^6 and m are as defined in claim 1), or a salt thereof.

30. The thiazole compound according to claim 1, wherein u is 1; R^1 and R^2 combine to form a benzene ring which may optionally be substituted by a member selected from a lower alkyl, a lower alkoxy, a nitro, an amino having optionally a lower alkyl substituent, or a halogen atom; and R^3 is a group of the formula:



(wherein A, Z, s, R^5, R^6 and m are as defined in claim 1), or a salt thereof.

31. The thiazole compound according to any one of claims 2, 3, 6-15, and 17-30, wherein the heterocyclic group for R^{11a} is a member selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholino, 1-azacyclooctyl, homopiperazinyl, homomorpholino, 1,4-diazabicyclo[4.3.0]nonyl, 1,4-diazabicyclo[4.4.0]decyl, pyridyl, 1,2,5,6-tetrahydropyridyl, thienyl, 1,2,4-triazolyl, 1,2,3,4-tetrazolyl, 1,3,4-triazolyl, quinolyl, 1,4-dihydroquinolyl, benzothiazolyl, pyrazyl, pyrimidyl, pyridazyl, pyrrolyl, pyrrolinyl, carbostyril, 1,3-dioxolanyl, thiomorpholino, 3,4-dihydrocarbostyril, 1,2,3,4-tetrahydroquinolyl,

2,3,4,5-tetrahydrofuryl, indolyl, isoindolyl, 3H-indolyl, indolinyl, indolidinyl, indazolyl, benzimidazolyl, benzoxazolyl, imidazolinyl, imidazolidinyl, isoquinolyl, naphthylidinyl, quinazolidinyl, quinoxalinyl, cinnolinyl, phthalazinyl, chromanyl, isoindolinyl, isochromanyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, thienyl, imidazolyl, pyrazolidinyl, benzofuryl, 2,3-dihydrobenzo[b]furyl, benzothienyl, tetrahydropyranyl, 4H-chromenyl, 1H-indazolyl, isoindolinyl, 2-imidazolinyl, 2-pyrrolinyl, furyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, pyranyl, pyrazolidinyl, 2-pyrazolinyl, quinuclidinyl, 1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 1,4-benzothiazinyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinoxalinyl, 1,3-dithia-2,4-dihydronaphthalenyl, 1,4-dithianaphthalenyl, 2,5-dihydrofurano[3,4-c]pyridyl, 2,3,4,5,6,7-hexahydro-1H-azepinyl, 1,2,3,4,5,6,7,8-octahydroazocinyl, 1,2,3,4,5,6-hexahydrooxepinyl, 1,3-dioxolanyl, 3,4,5,6-tetrahydro-2H-pyranyl, and 5,6-dihydro-2H-pyranyl.

32. A thiazole compound selected from the group consisting of

(1) 2-{(3-methoxy-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(2) 2-{(2-isopropyl-4-(3-(4-(4-methyl-1-piperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(3) 2-{(2-methoxy-4-(3-(2-(4-methyl-1-piperazinyl)-methyl-4-morpholinocarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(4) 2-{(2-ethoxy-4-(3-(4-(4-methyl-1-piperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(5) 2-{(3-methyl-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(6) 2-{(3-methoxy-6-ethyl-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(7) 2-{(3-methoxy-6-ethyl-4-(3-(4-methyl-1-piperazinyl)acryloyl)-phenoxy)methylcarbonylamino}benzothiazole,

(8) 2-{(2-trifluoromethyl-4-(3-(4-hydroxy-1-piperazinyl)acryloyl)-phenoxy)methylcarbonylamino}benzothiazole,

(9) 2-{(2-fluoro-4-(3-(2-(4-methyl-1-piperazinyl)methyl-4-morpholino-carbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(10) 2-{(2-methoxy-4-(3-(4-(4-methyl-1-piperazinyl)-1-piperidinyl-carbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(11) 2-{(2,3-dimethyl-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(12) 2-{(3-methoxy-4-(3-(4-(3,4-dimethyl-1-piperazinyl)-1-piperidinyl-carbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(13) 2-{(3-methoxy-6-isopropyl-4-(3-(4-methyl-1-piperazinyl)-carbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

(14) 2-{(2-methoxy-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinylcarbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

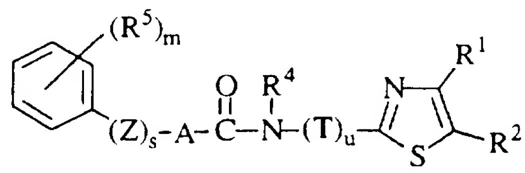
(15) 2-{(2-n-butyl-4-(3-(4-(4-methyl-1-homopiperazinyl)-1-piperidinyl-carbonyl)acryloyl)phenoxy)methylcarbonylamino}benzothiazole,

or a salt thereof.

33. A protein kinase C inhibitor which comprises as an active ingredient a thiazole compound or a salt thereof as set forth in claim 1.

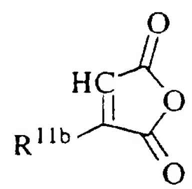
34. A process for preparing a thiazole compound as set forth in claim 1, which comprises the following steps of

(a) reacting a compound of the formula (2):



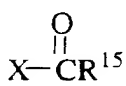
(2)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, with a compound of the formula (3):



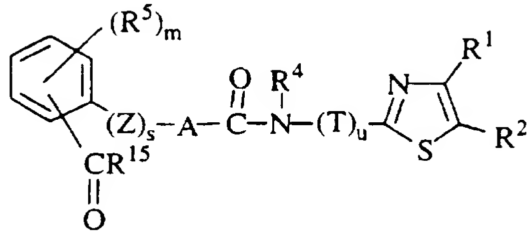
(3)

wherein R^{11b} is the same as defined in claim 1, or a compound of the formula (4):



(4)

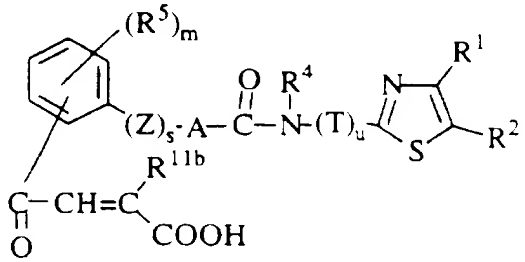
wherein R^{15} is a group: $-CH=C(R^{11b})(COR^{16})$ (R^{11b} is the same as defined in claim 1, and R^{16} is a hydroxy group or a lower alkoxy group), or a group: $-C{\equiv}C-COR^{14}$ (R^{14} is the same as defined in claim 1), and X is a halogen atom, to give a compound of the formula (1a):



(1a)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{15} is the same as defined above;

(b) reacting a compound of the formula (1b):

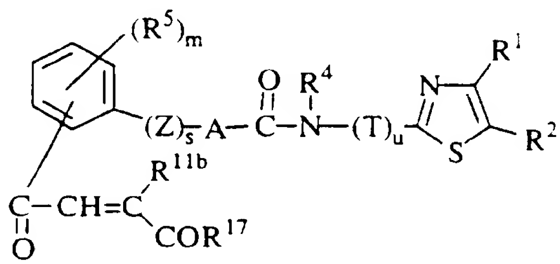


(1b)

wherein R^1, R^2, R^4, R^5, R^{11b}, Z, m, s, T, u and A are the same as defined in claim 1,, with a compoud of the formula (5):

$$R^{17}H \qquad (5)$$

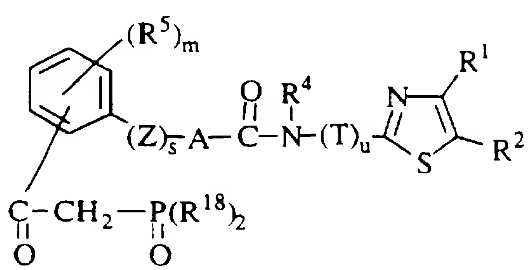
wherein R^{17} is the heterocyclic residues as defined for R^{11a} but having at least one $-N<$ in the heterocyclic nucleus, to give a compoud of the formula (1c):



(1c)

wherein R^1, R^2, R^4, R^5, R^{11b}, Z, m, s, T, u and A are the same as defined in claim 1, and R^{17} is the same as defined above;

(c) reacting a compound of the formula (10):

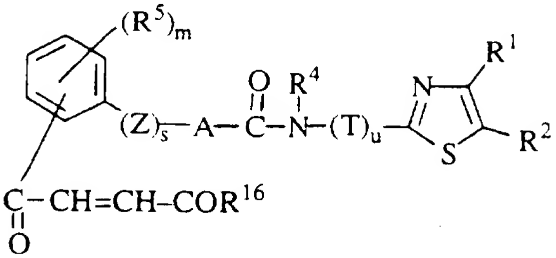


(10)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, R^{18} is a lower alkoxy group, with a compound of the formula (12):

$$R^{16}\underset{\overset{\|}{O}}{C}-CHO \qquad (12)$$

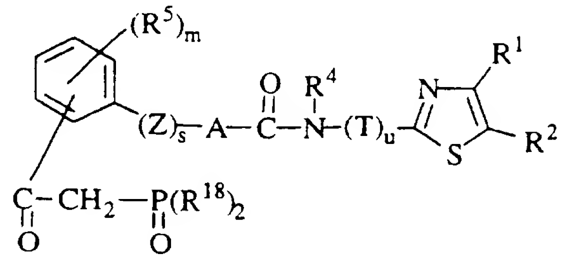
wherein R^{16} is the same as defined above, to give a compound of the formula (1d):



(1d)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1 and R^{16} is the same as defined above;

(d) reacting a compound of the formula (10):



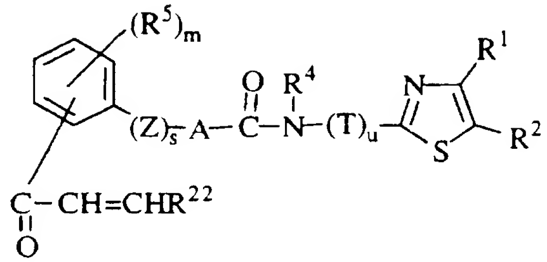
(10)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{18} is the same as defined above, with a compound of the formula (20):

$$R^{22}CHO \qquad (20)$$

wherein R^{22} is R^{22} is a 5- to 10-membered, saturated or unsaturated heteromono-

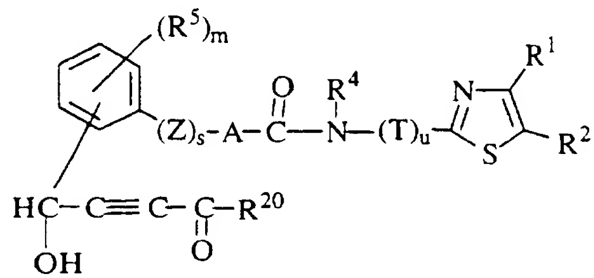
cyclic, heterobicyclic residue (said heterocyclic residue optionally having 1 to 3 substituents selected from (i) a lower alkyl group; (ii) a group: $-(B)_{\ell}$-$NR^{12}R^{13}$ (ℓ is the same as defined above, B is a group: –CO–A– (A is the same as defined above), a carbonyl group or a lower alkylene group, R^{12} and R^{13} are the same or different, and each are a hydrogen atom, a lower alkyl group, an amino-substituted lower alkyl group having optionally a lower alkyl substituent, or combine together with the adjacent nitrogen atom to which they bond to form a 5- to 12-membered saturated heteromonocyclic, heterobicyclic or hetero-sprio ring with or without being intervened with another nitrogen atom or an oxygen atom, said heterocyclic group may optionally have a substituent selected from a lower alkyl group, a lower alkoxycarbonyl group, a lower alkoxy-substituted lower alkyl group, an amino group having optionally a lower alkyl substituent and a hydroxy-substituted lower alkyl group); (iii) a lower alkoxycarbonyl group; (iv) a hydroxy-substituted lower alkyl group; (v) a pyridyl group being optionally sibstituted by a lower alkyl group having optionally a halogen substituent on the pyridine ring; (vi) a halogen-substituted lower alkyl group; (vii) a lower alkoxy group; (viii) a cycloalkyl group; (ix) a hydoxy group; (x) a tetrahydropyranyloxy-substituted lower alkyl group; (xi) a pyrimidyl group; (xii) a lower alkoxy-substituted lower alkyl group; (xiii) a carboxyl group; (xiv) a phenyl-lower alkoxy group; (xv) a phenyl-lower alkyl group having optio: .lly a lower alkylenedioxy substituent on the phenyl ring; (xvi) a lower alkanoyloxy group; and (xvii) a piperidinyl group having optionally a lower alkyl substituent on the piperidine ring, to give a compound of the formula (1h):



(1h)

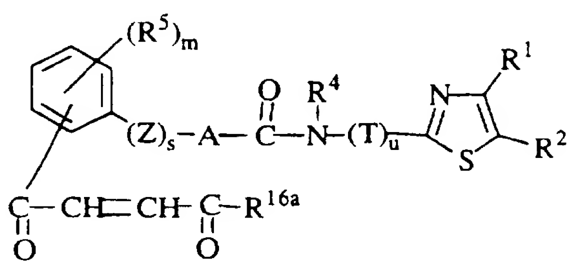
wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{18} and R^{22} are the same as defined above;

(e) converting a compound of the formula (11):



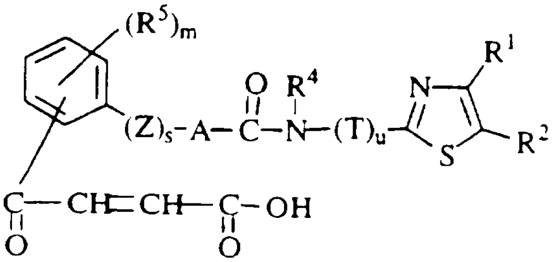
(11)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{20} is a lower alkoxy group, into a compound of the formula (1d'):



(1d')

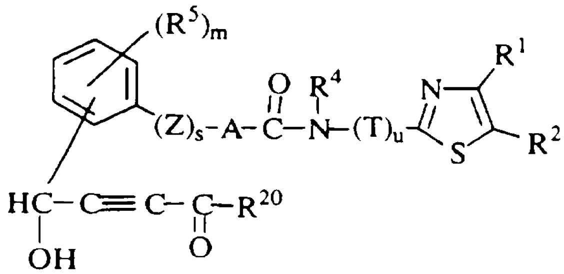
wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{16a} is a lower alkoxy group, in the presence of a basic compound, optionally followed by converting the compound (1d') into a compound of the formula (1e):



(1e)

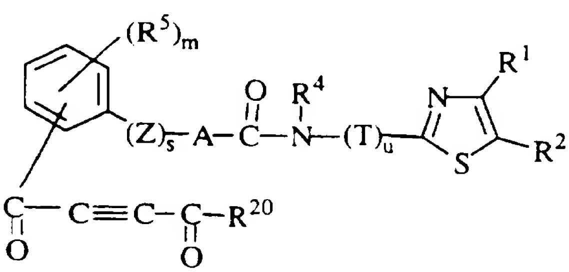
wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, in the presence of an acid or a basic compound;

(f) converting a compound of the formula (11):



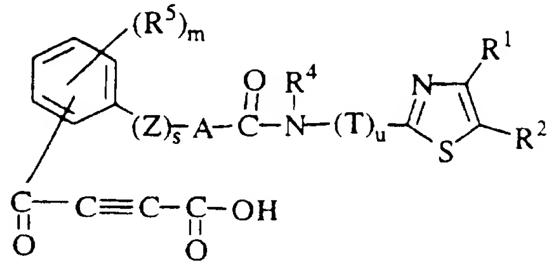
(11)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{20} is a lower alkoxy group, into a compound of the formula (1f):



(1f)

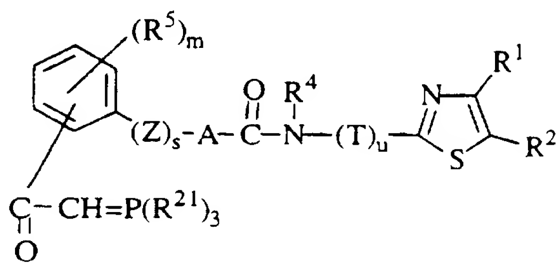
wherein R^1, R^2, R^4, R^5, Z, m, s, T, u, and A are the same as defined in claim 1, and R^{20} is the same as defined above, in the presence of an oxidizing agent, optionally followed by converting the compound (1f) into a compound of the formula (1g):



(1g)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, in the presence of an acid or a basic compound;

(g) reacting a compound of the formula (19):

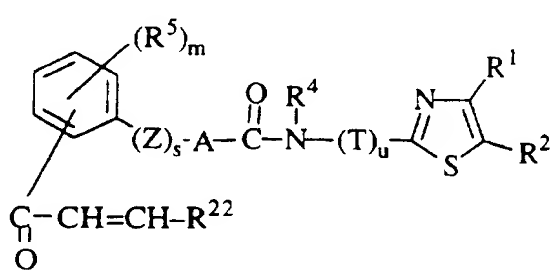


(19)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and R^{21} is a phenyl group, with a compound of the formula (20):

$R^{22}CHO$ (20)

wherein R^{22} is the same as defined above, to give a compound of the formula (1h):

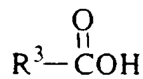


(1h)

wherein R^1, R^2, R^4, R^5, Z, m, s, T, u and A are the same as defined in claim 1, and

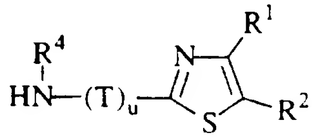
R^{22} is the same as defined above;

(h) reacting a compound of the formula (23):



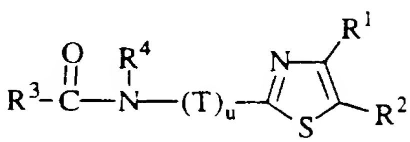
(23)

wherein R^3 is the same as defined in claim 1, with a compound of the formula (24):



(24)

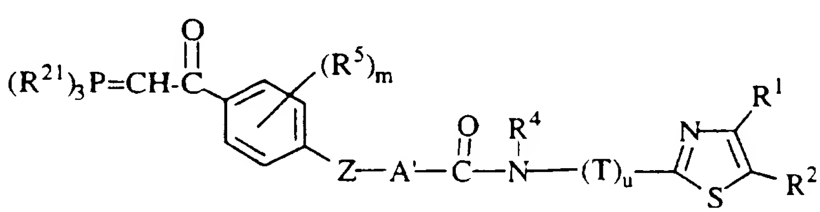
wherein R^1, R^2, R^4, T and u are the same as defined in claim 1, to give a compound of the formula (1):



(1)

wherein R^1, R^2, R^3, R^4, T and u are the same as defined in claim 1;

(i) reacting a compound of the formula (19a):

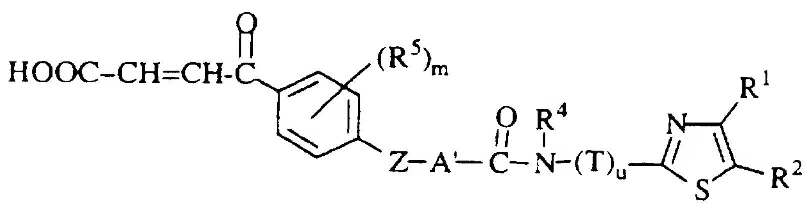


(19a)

wherein T, u, R^1, R^2, R^4, Z, R^5 and m are the sa[illegible] as defined in claim 1, and R^{21} is the same as defined above, and A' is a lower alkylene group, with a compound of the formula (44):

OHC·COOH (44)

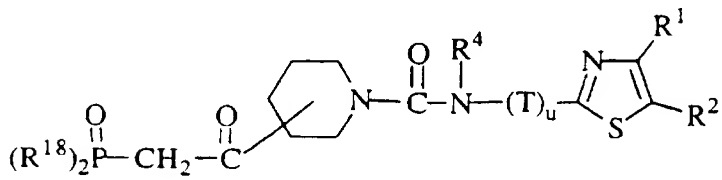
to give a compound of the formula (1q):



(1q)

wherein T, u, R^1, R^2, R^4, A', Z, R^5 and m are the same as defined in claim 1;

(j) reacting a compound of the formula (54):

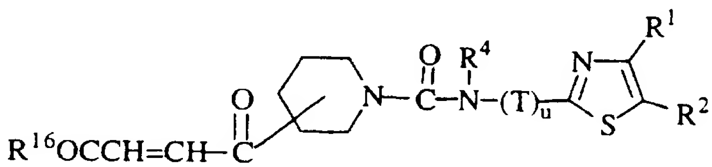


(54)

wherein R^1, R^2, T, u and R^4 are the same as defined in claim 1, and R^{18} is the same as defined above, with a compound of the formula (12):

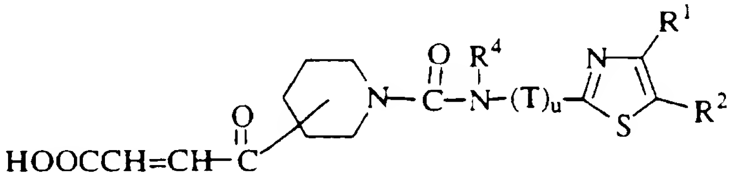
$$R^{16}\overset{O}{\overset{\|}{C}}CHO \quad (12)$$

wherein R^{16} is the same as defined above, to give a compound of the formula (1s):



(1s)

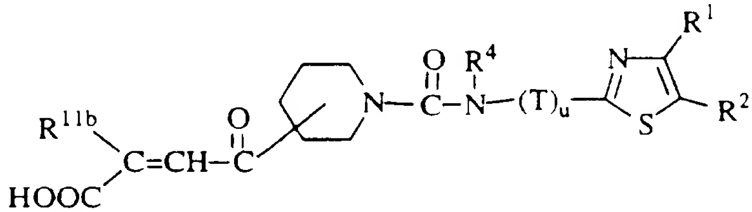
wherein R^1, R^2, T, u and R^4 are the same as defined in claim 1, and R^{16} is the same as defined above, optionally followed by converting the compound (1s) into a compound of the formula (1t):



(1t)

wherein R^1, R^2, T, u and R^4 are the same as defined in claim 1;

(k) reacting a compound of the formula (1u):

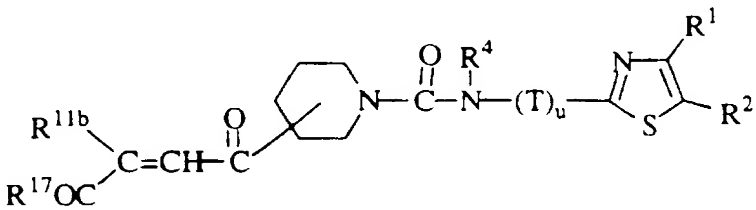


(1u)

wherein R^1, R^2, T, u, R^4 and R^{11b} are the same as defined in claim 1, with a compound of the formula (5):

$R^{17}H$ (5)

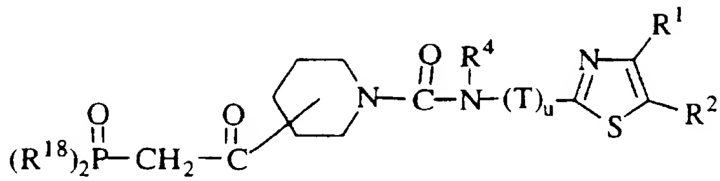
wherein R^{17} is the same as defined above, to give a compound of the formula (1v):



(1v)

wherein R^1, R^2, T, u, R^4 and R^{11b} are the same as defined in claim 1, and R^{17} is the same as defined above; or

(*ℓ*): reacting a compound of the formula (54):

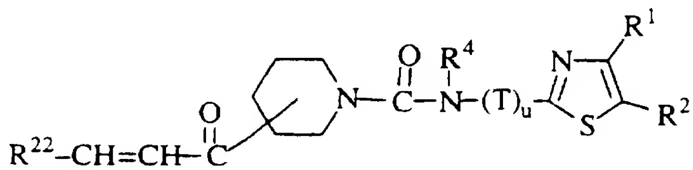


(54)

wherein R^1, R^2, T, u, R^4 and R^{18} are the same as defined above, with a compound of the formula (20):

$$R^{22}CHO \qquad (20)$$

wherein R^{22} is the same as defined above, to give a compound of the formula (1w):



(1w)

wherein R^1, R^2, T, u and R^4 are the same as defined in claim 1, and R^{22} is the same as defined above.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/02609

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/82 A61K31/425 C07D417/12 C07D277/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 638 564 A (ASAHI KASEI KOGYO K.K.) 15 February 1995 see the whole document ---	1,33
A	EP 0 343 893 A (PFIZER INC.) 29 November 1989 see claims ---	1,33
A	EP 0 412 404 A (FUJISAWA PHARMACEUTICAL CO) 13 February 1991 see claims -----	1,33

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1997	-7. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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